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SUBACUTE BACTERIAL ENDOCARDITIS*

A Report of Two Cases Successfully Treated with Penicillin

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With the Technical Assistance of Mary Meyeserian

BOSTON

THE medical literature contains reports of many cases of subacute bacterial endocarditis treated with penicillin.[1–14] Nevertheless, we are prompted to contribute reports of 2 additional cases. In the first place, all carefully studied cases treated with penicillin should be reported irrespective of their therapeutic outcome,§ so that by the accumulation of data on large numbers of cases, it will be possible to evaluate adequately the various aspects of this remarkable treatment and to explain the reasons for failure, which still occurs in about 25 to 30 per cent of cases. Secondly, certain features of these 2 cases show interesting contrasts and comparisons. Finally, the penicillin resistance of the *Streptococcus viridans* isolated from the blood in one of the cases was apparently greater than that of the originally isolated causative organism responsible for any other successfully treated case reported so far in the medical literature.[6–14]

CASE 1. G. T. (H.G.S. 6465), a 16-year-old girl, suffered her only definite attack of rheumatic fever at the age of 8 years. During this episode she was treated at the House of the Good Samaritan, and later she was examined periodically in the Out-Patient Department of the Children's Hospital and in the Rheumatic-Fever Clinic of the Massachusetts General Hospital. From the time of discharge from the House of the Good Samaritan until the onset of her last illness she remained essentially well except for occasional nosebleeds and colds. There was never any clinical evidence of active rheumatic fever, and the blood sedimentation rate remained normal.

The present illness began on June 13, 1944, when the patient went swimming. Soon after arriving home, she had a chill. Chills continued off and on for 2 or 3 days, and migratory joint pains developed. Pains in the muscles of the right upper arm also occurred. There was no history of tooth extraction or other dental work and no respiratory infection prior to the onset of this illness.

On July 20 examination revealed an oral temperature of 103.2°F. The patient appeared thin and pale. The heart was borderline in size, the apex impulse being about in the midclavicular line. There was a loud systolic murmur at the mitral area. There were no diastolic murmurs. There were no petechiae, but the spleen was easily palpable. Because of the enlarged spleen, subacute bacterial endocarditis was suspected.

Because of an unavoidable delay the patient was not admitted to the House of the Good Samaritan until August 25. During the 1st week at the hospital she was obviously extremely ill. The rectal temperature reached daily peaks of 102.5 to 104.5°F. At times she was lethargic, and sometimes she was delirious. There was moderate pallor. Several tender red spots appeared from time to time over the tips of the fingers and toes. The heart was of borderline size, and the rhythm was regular. The heart rate was rapid and varied from 110 to 140 per minute. There was a loud, widely transmitted, mitral systolic murmur. There were no diastolic murmurs. The abdomen was examined with difficulty because of marked tenderness and spasm in the left upper quadrant. After a few days the spasm lessened, and the spleen was definitely felt. The electrocardiogram was essentially normal except for sinus tachycardia. The PR interval was 0.16 second. The corrected sedimentation rate (Rourke-Ernstene method) ranged between 1.2 and 1.5 mm. per minute.

Examination of the blood showed a red-cell count of 3,500,000, with a hemoglobin (photoelectric) of 9.4 gm., and a white-cell count varying from 9000 to 12,000, with 60 per cent neutrophils, 28 per cent lymphocytes, 8 per cent monocytes and 4 per cent eosinophils. The hematocrit reading was 33. The antistreptolysin titer was 125 units. The centrifuged sediment of a single urine specimen showed 5 red cells per high-power field; otherwise numerous urine specimens were negative. The specific gravity ranged from 1.017 to 1.030. Five successive daily blood cultures beginning on August 26 were positive for *Streptococcus viridans*. The organism isolated from these cultures was inhibited in vitro by as little as 0.02 unit of penicillin per cubic centimeter; even a heavy inoculum was inhibited by 0.06 unit.

Penicillin therapy was started on August 31. Intramuscular injections of 37,500 units were given every 3 hours, making a total of 300,000 units every 24 hours. This treatment was continued for 14 days. On September 14, the dose was reduced to 12,500 units intramuscularly every 3 hours, totaling 100,000 units every 24 hours. This reduced dosage was continued for 10 days, when the penicillin therapy was discontinued. During the 24 days of treatment the patient received a total of 5,000,000 units of penicillin. Penicillin blood levels were determined on several occasions on specimens taken 3 hours after the previous injection and just prior to the next injection. On all these occasions the concentration was less than 0.06 unit per cubic centimeter of serum.

The response to penicillin therapy was dramatic. Within 24 hours of the first injection the fever lessened, and the downward trend continued until September 6, when the rectal temperature failed to rise above 100°F. Thereafter the temperature remained normal except for an unexplained period in which the rectal temperature reached 102.5°F. This

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febrile episode began on September 15, the day after the 24-hour penicillin dosage had been reduced from 300,000 to 100,000 units, but subsided within 3 days, and thereafter the rectal temperature remained well under 100°F. The patient began to feel better almost immediately after treatment was begun, and her general appearance improved rapidly. The tenderness in the left upper quadrant of the abdomen soon disappeared, but the spleen remained readily palpable until January 23, 1945. Thereafter it could be felt only occasionally just below the left costal margin. The frequency with which small, tender, red spots occurred on the fingers and toes lessened noticeably by September 13, 1944. Occasional spots continued to appear, however, as long as 3 months after the treatment was discontinued.

The corrected sedimentation rate gradually lessened but did not fall within the upper normal limit of 0.4 mm. per minute until October 23, after which it remained well within normal limits. The anemia likewise improved; by November 13, the hematocrit reading was 43. The first blood culture after the onset of therapy was taken on September 2 and was sterile. Seven additional cultures during the course of penicillin injections and 32 others after termination of treatment were also sterile.

After discharge from the ward on February 11, the patient was examined at intervals of 1 or 2 months at the Follow-up Clinic and was last seen on September 25, 1946. During this entire period she was feeling extremely well, attending school and leading an essentially normal life. Physical examination remained entirely negative except for the cardiac findings, which had not changed. The corrected sedimentation rate was found to be well within normal limits (less than 0.4 mm. per minute), and the blood cultures remained sterile. During the total follow-up period of 24 months since discontinuation of therapy, there was a total of forty-four sterile blood cultures.

Case 2. M.A. (H.G.S.4432), a 27-year-old woman, was admitted to the House of the Good Samaritan for the first time on March 10, 1927, when she was 8 years old, during her only definite attack of rheumatic fever. Following discharge, she was entirely well and was able to lead a physically active life. She was examined on occasion in the Out-Patient Department of the Boston City Hospital until October 10, 1939. Thereafter follow-up examinations were continued at intervals at the House of the Good Samaritan clinic. On December 2, 1943, the heart was described as borderline in size, the apex impulse being in the 5th intercostal space 7.5 cm. to the left of the midsternal line and just about in the midclavicular line. The rhythm was regular. There was a fairly loud (Grade 3), somewhat harsh, systolic murmur maximum at the apex, where the mitral 1st sound was masked. There were no definite diastolic murmurs.

In May, 1944, without any preceding respiratory infection, tooth extraction or other unusual event, the patient began to feel tired and developed migratory joint pains. In spite of these symptoms she did not remain in bed for any long period until July 1, when the left ankle became swollen and so painful that she could not walk. About a week later she had lower abdominal pain and for the first time noticed fever, the temperature reaching 102°F. (oral). Within a few days these symptoms subsided, but pain in the left buttock and in the left side of the chest soon developed. The chest pain was aggravated by deep breathing. An x-ray film revealed no abnormalities. Mild fever returned and continued in a variable fashion thereafter.

Examination of the patient at home on August 29 revealed an oral temperature of 99.6°F. Three small, nontender red spots and a tender area of purplish discoloration were seen on the extremities. The cardiac findings were essentially the same as those described at the last previous clinic visit on December 2.

A diagnosis of probable subacute bacterial endocarditis was made, and the patient was admitted to the House of the Good Samaritan on September 5. For a period of 23 days — from September 5 to September 28 — during which therapy was withheld so that adequate observations could be made, the patient felt fairly well and did not appear very ill. There was a low-grade fever, the daily maximum rectal temperature varying from 100.2 to 101.0°F. Several petechiae appeared during this period. On the morning of September 28, prior to the initiation of therapy, a painful, tender, purplish discoloration, several centimeters in diameter, appeared over the 4th toe of the left foot. At no time could the spleen be felt. The electrocardiogram was normal and had a PR interval of 0.14 second. The corrected sedimentation rate varied from 0.55 to 0.92 mm. per minute. Examination of the blood showed a red-cell count of 3,800,000, with a hemoglobin (photoelectric) of 10.2 gm., and a white-cell count varying from 4700 to 8000, with 67 per cent neutrophils, 29 per cent lymphocytes, 1 per cent endothelial cells and 3 per cent eosinophils. The hematocrit reading varied from 31 to 33. The antistreptolysin titer was 200 units. Eight urine specimens were essentially negative and showed no evidence of microscopic hematuria; the specific gravity varied from 1.017 to 1.024.

Ten consecutive blood cultures taken prior to therapy consistently gave a pure growth of *Str. viridans*. In vitro studies showed that inhibition of growth of this organism required at least 0.40 unit of penicillin per cubic centimeter. With even high concentrations of penicillin, complete or nearly complete sterility could be obtained only if a highly diluted culture was used for the inoculum.

Penicillin therapy was begun on September 28. It was obvious from the in vitro studies that the causative organism was relatively resistant to penicillin and that, to obtain adequate blood levels, larger amounts of penicillin than had been customary at that time would be necessary. For the purpose of obtaining information concerning the relation of blood concentration to dosage, however, an initial daily dose of 240,000 units was given, and this was gradually increased to a maximum of 960,000 units by October 5. During these first 8 days of therapy the penicillin was given intramuscularly every hour in divided doses. On October 6 the method of administration was changed to constant intramuscular drip. For 24 hours, 600,000 units of penicillin were given in this way, and thereafter 960,000 units were given every 24 hours until the medication was discontinued on October 12. The total duration of penicillin therapy was 14 days, and the total amount of penicillin administered was 10,000,000 units. Table 1 presents the details of the therapy and the penicillin concentrations in the serum of blood collected either 45 minutes after an intramuscular injection or during constant intramuscular administration. Following the discontinuation of penicillin therapy, the patient was kept under observation in the hospital for 10 weeks until discharge on December 24.

Table 1. *Method of Administration, Dosage and Serum Concentration of Penicillin in Case 2.*

Date	Administration by Hourly Intramuscular Injection			Administration by Intramuscular Drip	
	Dose	24-hour dosage	Serum concentration	24-hour dosage	Serum concentration
	units	*units*	*units per cc.*	*units*	*units per cc*
9/28- 9/29	10,000	240,000	0.10		
9/29- 9/30	15,000	60,000	0.16		
9/30-10/ 1	15,000	360,000	0.15		
10/ 1-10/ 2	20,000	480,000	0.25		
10/ 2-10/ 3	25,000	600,000	0.33		
10/ 3-10/ 4	30,000	720,000	0.68		
10/ 4-10/ 5	35,000	840,000	0.88		
10/ 5-10/ 6	40,000	960,000	0.58		
			0.97		
			1.10		
			0.68		
10/ 6-10/ 7				600,00	0.10
					0.35
					0.50
10/ 7-10/ 8				960,000	0.69
10/ 8-10/ 9				960,000	0.91
10/ 9-10/10				960,000	0.91
10/10-10/11				960,000	0.73
					0.73
10/11-10/12				960,000	0.70

Within 48 hours after the initiation of penicillin therapy, the rectal temperature failed to rise above 100°F. and thereafter remained within normal limits. There were no further joint pains, and the patient remained entirely free of symptoms. One small, tender, red spot appeared on the tip of the left little finger on October 5, but no evidence of emboli occurred thereafter. The corrected sedimentation rate dropped to 0.39 mm. per minute on October 23 or 25 days after the onset of therapy, and subsequently remained well within normal limits. A blood culture on September 29, taken 1 hour after the last previous intramuscular injection of 10,000 units of penicillin, was still positive for *Str. viridans*,

and another culture on September 30, taken 1 hour after the previous injection of 15,000 units, was likewise positive. The next ten consecutive cultures taken during therapy, however, failed to show streptococci. From the time the therapy was discontinued on October 12 until the time the patient was discharged on December 24, fourteen additional negative cultures were obtained.

Following discharge from the hospital the patient was examined every 1 or 2 months in the Follow-up Clinic. She remained entirely symptom free and, when last seen on October 9, 1946, was leading a normal active life. The cardiac findings remained essentially the same as those described above. Otherwise, physical examination revealed no abnormalities. At all visits the corrected sedimentation rate was well within normal limits and the blood cultures showed no growth. During a total follow-up period of 24 months since discontinuation of therapy, twenty-seven consecutive blood cultures were negative.

Discussion

The clinical backgrounds in these cases were rather similar. Both patients were relatively young women who had developed rheumatic heart disease following a single attack of rheumatic fever early in childhood; both had been observed at the House of the Good Samaritan during the original attacks of rheumatic fever, and both had been examined at intervals thereafter in the clinics of various hospitals. In both cases the valvular lesion was only that of mitral regurgitation, and the heart was of normal size or slightly enlarged. Until the onset of the bacterial infection both patients had been physically active and able to lead normal lives. In neither case could a history be elicited of preceding dental work or respiratory infection.

The clinical course of the bacterial endocarditis, however, was not the same for these patients. The illness in Case 1 began rather suddenly with a chill about two months before admission. From the onset until the effect of penicillin therapy the patient was acutely ill, with a high fever and a rapid heart rate. On admission to the House of the Good Samaritan, she was at times lethargic and at other times delirious. On the other hand, the illness in Case 2 began rather insidiously about four months before admission to the hospital. The patient had persistent symptoms, but at no time did she have a high fever or seem acutely ill. The serum antistreptolysin titers, as might be expected, were low in both cases.

The organisms isolated from both patients were classified as *Str. viridans* on the basis of the appearance of their colonies on 5 per cent horse-blood agar plates. Serums for Lancefield grouping were not available in the laboratory at that time, and no other attempts were made to subclassify the strains.

The in vitro behavior of the organisms in the presence of penicillin was of particular interest. The streptococcus isolated in Case 1, in which the patient was acutely ill, was found to be highly susceptible to penicillin. Growth in broth was prevented by as little as 0.02 units per cubic centimeter, and in the presence of concentrations of penicillin slightly in excess of this even a heavy inoculum of the organisms could be completely or nearly completely sterilized within twenty-four hours. In contrast, the strain isolated in Case 2, in which the patient was mildly ill, was relatively resistant to penicillin. To prevent growth of the bacteria in broth it was necessary to have a concentration of 0.40 units of penicillin per cubic centimeter. Furthermore, the rate at which the organisms were killed even by an excess of penicillin was considerably slower with the strain in Case 2 than with that in Case 1. Thus, when penicillin-sensitivity tests were performed on the strain in the former, sterilization could be completely or nearly completely effected only if a relatively small inoculum was used. If the inoculum contained more than 20,000 organisms per cubic centimeter, sterilization could not be produced by even 100 units of penicillin, and after twenty-four hours of incubation numerous live organisms were still present. Further details and discussion of the in vitro behavior of these strains are included in a report published elsewhere.[15]

The patient in Case 1 was cured relatively easily with penicillin in moderate dosage given by intermittent intramuscular injections every three hours. This favorable result is what might have been expected from the knowledge of the high penicillin sensitivity of the causative organism. The persistence of small red spots for a period of sixteen weeks is of interest.

The excellent response of the patient in Case 2 to penicillin is more surprising. Even though she was clinically not acutely ill, the disease had been present for at least four months prior to the initiation of therapy, and as already pointed out, the infection was caused by an organism whose bacteriostatic sensitivity to penicillin was relatively poor in comparison to that of organisms isolated in most cases of subacute bacterial endocarditis. That a cure was actually obtained was probably due, at least in large part, to the fact that a high penicillin concentration in the blood was maintained almost constantly throughout the period of treatment. Concentrations above the bacteriostatic sensitivity level of 0.40 unit were present for most of the time after the first four days, and for a period of five or six days the serum concentration was at a level equal to nearly twice the bacteriostatic sensitivity of the organism.

Another interesting feature in Case 2 was the successful outcome after treatment for only two weeks. Although not necessarily contradictory, this result is particularly worthy of note in view of the opinion recently expressed by Bloomfield and Halpern[13] that penicillin therapy should be continued for at least two months.

There can be no doubt that these 2 cases represent true cures of subacute bacterial endocarditis. The diagnosis was firmly established on both clinical and bacteriologic grounds before therapy was instituted. Both patients had fever and multiple evidences of emboli, as well as repeated and consistently positive blood cultures for *Str. viridans*. Both patients responded promptly to therapy. All evidences

iodine metabolism. In 1942, Hertz and Roberts,[1] and also Hamilton and Lawrence,[2] rendered preliminary reports of the effects of therapy with radioactive iodine in the treatment of thyrotoxicosis. The results encouraged an extension of the studies by Hertz and Roberts.[3] On the basis of these observations, Chapman and Evans[4] were prompted to use larger doses of radioactive iodine than previously had been used in thyrotoxic patients.

The basis for such therapy arises from the fact that, since in untreated hyperthyroidism the thyroid gland can take up as much as 80 per cent of a small dose (less than 2 mg.) of iodide within a few hours after its administration, it is possible to obtain concentrated irradiation at the site desired without undue exposure of other tissues. Although the total number of patients treated with radioactive iodine is relatively small, the results of this type of treatment appear encouraging. Hertz and Roberts[3] report that, in 29 uniodinized patients with hyperthyroidism whose goiters weighed from 60 to 75 gm., radioactive iodine in doses of 5 to 25 millicuries cured the disease in about 80 per cent. Chapman and Evans[4] observed that, in 22 patients with hyperthyroidism whom they treated with larger amounts (14 to 52 millicuries) of radioactive iodine, 14 responded well to the single dose. Three were given two doses, and 5 were given three doses, and as a rule, the subsequent doses were larger than the first one. Four patients later developed myxedema, and 2 had a persistence of thyrotoxicosis following treatment, although the disease became less intense.

The chief problem in the use of radioactive iodine is to determine the optimal dose. The amount required depends on the amount of iodine in the body, the size of the thyroid gland, the nature of the pathologic changes in the gland and many other conditions. Inability to estimate these factors accurately makes it more difficult to select the proper dose than it is for the surgeon to decide how much of the thyroid tissue should be removed. In either instance, only a slight difference in the number of cells that are permitted to live may result in a persistence of the thyrotoxicosis or the development of myxedema. It appears wise to use a minimal dose of radioactive iodine, since additional doses can be given if needed; with excessive therapy some patients may develop permanent myxedema. Few other ill effects from the use of radioactive iodine therapy have been observed. Occasional patients have had transient reactions resembling roentgen-ray sickness. Whether this type of treatment predisposes to the development of cancer or whether structural damages will subsequently occur in other tissues remains to be ascertained.

The extent of usefulness of this form of therapy has not been determined. In certain complicated cases it is unquestionably the treatment of choice. Moreover, it appears to be useful in some patients who have been unsuccessfully treated with thiouracils and in those who have not obtained good results after having been subjected to surgical treatment. Indeed, it is possible that this form of therapy may become the one of choice in the majority of patients with thyrotoxicosis, but this can be established only on the basis of the findings in extended investigative studies.

References

1. Hertz, S., and Roberts, A. Application of radioactive iodine in therapy of Graves' disease. *J. Clin. Investigation* **21**:624, 1942.
2. Hamilton, J. G., and Lawrence, J. H. Recent clinical developments in therapeutic application of radio-phosphorus and radio-iodine. *J. Clin. Investigation* **21**:624, 1942.
3. Hertz, S., and Roberts, A. Radioactive iodine in study of thyroid physiology. *J. A. M. A.* **131**:81-86, 1946.
4. Chapman, E. M., and Evans, R. D. Radioactive iodine in hyperthyroidism. *J. A. M. A.* **131**:86-92, 1946.

NOTICES

NEW ENGLAND PEDIATRIC SOCIETY

A meeting of the New England Pediatric Society will be held on Wednesday, October 23, in Boston.

Program

12:00 m. Clinicopathological Conference of the Children's Hospital (held temporarily at the Peter Bent Brigham Hospital Amphitheater). Members of the Society are invited to attend.

1:15 p.m. Luncheon at Vanderbilt Hall, Harvard Medical School (price, 70 cents).

2:00 p.m. Regular Combined Clinic. Main Amphitheater, Children's Hospital.

3:00 p.m. Presentation of patients with tumors. Main Amphitheater, Children's Hospital. Members of the medical profession and students are invited to attend.

5:30 p.m. Refreshments at Longwood Towers.

6:30 p.m. Dinner at Longwood Towers (price, $2.50, including tax). Members of the Society and their guests are invited to attend.

7:30 p.m. Tumors in Infants and Children. Children's Hospital. Dr. Sidney Farber. Members of the medical profession and students are invited to attend.

NEW ENGLAND ROENTGEN RAY SOCIETY

The New England Roentgen Ray Society will hold its first meeting of the season on Friday, October 18, at the Hotel Beaconsfield, Brookline, Massachusetts. At 4:30 p.m. there will be an x-ray conference on diseases of the gastrointestinal tract. At 8:00 p.m. Dr. Frederic E. Templeton, of Seattle, Washington, will speak on "The Esophagus — Some Roentgenologic Observations on the Muscular Action in the Normal and Abnormal." Interested physicians are invited to attend.

(*Notices continued on page xiii*)

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In May, 1944, without any preceding respiratory infection, tooth extraction or other unusual event, the patient began to feel tired and developed migratory joint pains. In spite of these symptoms she did not remain in bed for any long period until July 1, when the left ankle became swollen and so painful that she could not walk. About a week later she had lower abdominal pain and for the first time noticed fever, the temperature reaching 102°F. (oral). Within a few days these symptoms subsided, but pain in the left buttock and in the left side of the chest soon developed. The chest pain was aggravated by deep breathing. An x-ray film revealed no abnormalities. Mild fever returned and continued in a variable fashion thereafter.

Examination of the patient at home on August 29 revealed an oral temperature of 99.6°F. Three small, nontender red spots and a tender area of purplish discoloration were seen on the extremities. The cardiac findings were essentially the same as those described at the last previous clinic visit on December 2.

A diagnosis of probable subacute bacterial endocarditis was made, and the patient was admitted to the House of the Good Samaritan on September 5. For a period of 23 days — from September 5 to September 28 — during which therapy was withheld so that adequate observations could be made, the patient felt fairly well and did not appear very ill. There was a low-grade fever, the daily maximum rectal temperature varying from 100.2 to 101.0°F. Several petechiae appeared during this period. On the morning of September 28, prior to the initiation of therapy, a painful, tender, purplish discoloration, several centimeters in diameter, appeared over the 4th toe of the left foot. At no time could the spleen be felt. The electrocardiogram was normal and had a PR interval of 0.14 second. The corrected sedimentation rate varied from 0.55 to 0.92 mm. per minute. Examination of the blood showed a red-cell count of 3,800,000, with a hemoglobin (photoelectric) of 10.2 gm., and a white-cell count varying from 4700 to 8000, with 67 per cent neutrophils, 29 per cent lymphocytes, 1 per cent endothelial cells and 3 per cent eosinophils. The hematocrit reading varied from 31 to 33. The antistreptolysin titer was 200 units. Eight urine specimens were essentially negative and showed no evidence of microscopic hematuria; the specific gravity varied from 1.017 to 1.024.

Ten consecutive blood cultures taken prior to therapy consistently gave a pure growth of *Str. viridans*. In vitro studies showed that inhibition of growth of this organism required at least 0.40 unit of penicillin per cubic centimeter. With even high concentrations of penicillin, complete or nearly complete sterility could be obtained only if a highly diluted culture was used for the inoculum.

Penicillin therapy was begun on September 28. It was obvious from the in vitro studies that the causative organism was relatively resistant to penicillin and that, to obtain adequate blood levels, larger amounts of penicillin than had been customary at that time would be necessary. For the purpose of obtaining information concerning the relation of blood concentration to dosage, however, an initial daily dose of 240,000 units was given, and this was gradually increased to a maximum of 960,000 units by October 5. During these first 8 days of therapy the penicillin was given intramuscularly every hour in divided doses. On October 6 the method of administration was changed to constant intramuscular drip. For 24 hours, 600,000 units of penicillin were given in this way, and thereafter 960,000 units were given every 24 hours until the medication was discontinued on October 12. The total duration of penicillin therapy was 14 days, and the total amount of penicillin administered was 10,000,000 units. Table 1 presents the details of the therapy and the penicillin concentrations in the serum of blood collected either 45 minutes after an intramuscular injection or during constant intramuscular administration. Following the discontinuation of penicillin therapy, the patient was kept under observation in the hospital for 10 weeks until discharge on December 24.

Table 1. *Method of Administration, Dosage and Serum Concentration of Penicillin in Case 2.*

Date	Administration by Hourly Intramuscular Injection			Administration by Intramuscular Drip	
	dose	24-hour dosage	serum concentration	24-hour dosage	serum concentration
	units	*units*	*units per cc.*	*units*	*units per cc*
9/28- 9/29	10,000	240,000	0.10		
9/29- 9/30	15,000	360,000	0.16		
9/30-10/ 1	15,000	360,000	0.15		
10/ 1-10/ 2	20,000	480,000	0.25		
10/ 2-10/ 3	25,000	600,000	0.33		
10/ 3-10/ 4	30,000	720,000	0.68		
10/ 4-10/ 5	35,000	840,000	0.88		
10/ 5-10/ 6	40,000	960,000	0.58		
			0.97		
			1.10		
			0.68		
10/ 6-10/ 7				600,00	0.10
					0.35
					0.50
10/ 7-10/ 8				960,000	0.69
10/ 8-10/ 9				960,000	0.91
10/ 9-10/10				960,000	0.91
10/10-10/11				960,000	0.73
					0.73
10/11-10/12				960,000	0.70

Within 48 hours after the initiation of penicillin therapy, the rectal temperature failed to rise above 100°F. and thereafter remained within normal limits. There were no further joint pains, and the patient remained entirely free of symptoms. One small, tender, red spot appeared on the tip of the left little finger on October 5, but no evidence of emboli occurred thereafter. The corrected sedimentation rate dropped to 0.39 mm. per minute on October 23 or 25 days after the onset of therapy, and subsequently remained well within normal limits. A blood culture on September 29, taken 1 hour after the last previous intramuscular injection of 10,000 units of penicillin, was still positive for *Str. viridans*,

and another culture on September 30, taken 1 hour after the previous injection of 15,000 units, was likewise positive. The next ten consecutive cultures taken during therapy, however, failed to show streptococci. From the time the therapy was discontinued on October 12 until the time the patient was discharged on December 24, fourteen additional negative cultures were obtained.

Following discharge from the hospital the patient was examined every 1 or 2 months in the Follow-up Clinic. She remained entirely symptom free and, when last seen on October 9, 1946, was leading a normal active life. The cardiac findings remained essentially the same as those described above. Otherwise, physical examination revealed no abnormalities. At all visits the corrected sedimentation rate was well within normal limits and the blood cultures showed no growth. During a total follow-up period of 24 months since discontinuation of therapy, twenty-seven consecutive blood cultures were negative.

Discussion

The clinical backgrounds in these cases were rather similar. Both patients were relatively young women who had developed rheumatic heart disease following a single attack of rheumatic fever early in childhood; both had been observed at the House of the Good Samaritan during the original attacks of rheumatic fever, and both had been examined at intervals thereafter in the clinics of various hospitals. In both cases the valvular lesion was only that of mitral regurgitation, and the heart was of normal size or slightly enlarged. Until the onset of the bacterial infection both patients had been physically active and able to lead normal lives. In neither case could a history be elicited of preceding dental work or respiratory infection.

The clinical course of the bacterial endocarditis, however, was not the same for these patients. The illness in Case 1 began rather suddenly with a chill about two months before admission. From the onset until the effect of penicillin therapy the patient was acutely ill, with a high fever and a rapid heart rate. On admission to the House of the Good Samaritan, she was at times lethargic and at other times delirious. On the other hand, the illness in Case 2 began rather insidiously about four months before admission to the hospital. The patient had persistent symptoms, but at no time did she have a high fever or seem acutely ill. The serum antistreptolysin titers, as might be expected, were low in both cases.

The organisms isolated from both patients were classified as *Str. viridans* on the basis of the appearance of their colonies on 5 per cent horse-blood agar plates. Serums for Lancefield grouping were not available in the laboratory at that time, and no other attempts were made to subclassify the strains.

The in vitro behavior of the organisms in the presence of penicillin was of particular interest. The streptococcus isolated in Case 1, in which the patient was acutely ill, was found to be highly susceptible to penicillin. Growth in broth was prevented by as little as 0.02 units per cubic centimeter, and in the presence of concentrations of penicillin slightly in excess of this even a heavy inoculum of the organisms could be completely or nearly completely sterilized within twenty-four hours. In contrast, the strain isolated in Case 2, in which the patient was mildly ill, was relatively resistant to penicillin. To prevent growth of the bacteria in broth it was necessary to have a concentration of 0.40 units of penicillin per cubic centimeter. Furthermore, the rate at which the organisms were killed even by an excess of penicillin was considerably slower with the strain in Case 2 than with that in Case 1. Thus, when penicillin-sensitivity tests were performed on the strain in the former, sterilization could be completely or nearly completely effected only if a relatively small inoculum was used. If the inoculum contained more than 20,000 organisms per cubic centimeter, sterilization could not be produced by even 100 units of penicillin, and after twenty-four hours of incubation numerous live organisms were still present. Further details and discussion of the in vitro behavior of these strains are included in a report published elsewhere.[15]

The patient in Case 1 was cured relatively easily with penicillin in moderate dosage given by intermittent intramuscular injections every three hours. This favorable result is what might have been expected from the knowledge of the high penicillin sensitivity of the causative organism. The persistence of small red spots for a period of sixteen weeks is of interest.

The excellent response of the patient in Case 2 to penicillin is more surprising. Even though she was clinically not acutely ill, the disease had been present for at least four months prior to the initiation of therapy, and as already pointed out, the infection was caused by an organism whose bacteriostatic sensitivity to penicillin was relatively poor in comparison to that of organisms isolated in most cases of subacute bacterial endocarditis. That a cure was actually obtained was probably due, at least in large part, to the fact that a high penicillin concentration in the blood was maintained almost constantly throughout the period of treatment. Concentrations above the bacteriostatic sensitivity level of 0.40 unit were present for most of the time after the first four days, and for a period of five or six days the serum concentration was at a level equal to nearly twice the bacteriostatic sensitivity of the organism.

Another interesting feature in Case 2 was the successful outcome after treatment for only two weeks. Although not necessarily contradictory, this result is particularly worthy of note in view of the opinion recently expressed by Bloomfield and Halpern[13] that penicillin therapy should be continued for at least two months.

There can be no doubt that these 2 cases represent true cures of subacute bacterial endocarditis. The diagnosis was firmly established on both clinical and bacteriologic grounds before therapy was instituted. Both patients had fever and multiple evidences of emboli, as well as repeated and consistently positive blood cultures for *Str. viridans*. Both patients responded promptly to therapy. All evidences

of inflammation, including the sedimentation rate, and all embolic phenomena eventually disappeared. Numerous blood cultures during and after treatment continued to be negative. Subsequent to discharge from the hospital the patients were examined every one or two months and were found to be clinically free from disease. Furthermore, the blood sedimentation rates were normal, and the blood cultures were negative at every clinic visit. The total follow-up since discontinuation of the penicillin therapy was twenty-four months for both patients and both were leading completely normal physically active lives.

Summary

Reports are presented of 2 cases in which the patients were cured of subacute bacterial endocarditis by penicillin therapy.

The penicillin resistance of the originally isolated causative organism in one case was greater than that of any other successfully treated case that has been reported in the medical literature.

The correlation of the clinical picture with the penicillin sensitivity of the causative organism is of interest: one patient was extremely ill, and the causative organism was extremely sensitive to penicillin; and the other was mildly ill, and the causative organism was relatively resistant to penicillin.

In one case a cure was obtained after only two weeks of penicillin therapy.

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HEMOSTASIS BY THROMBIN AND FIBRIN FOAM IN SUPRAPUBIC PROSTATECTOMY*

An Analysis of 40 Cases

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THE operative cure of the patient suffering from prostatic obstruction involves three major problems — control of renal function and disordered water balance, control of infection and control of hemorrhage at operation and subsequently.

Dehydration, which is often present in prostatic obstruction, has recently been clearly demonstrated to be responsive to various forms of parenteral fluid therapy based on the chemical determination of the blood electrolytes. A proper acid-base equilibrium of the blood and tissue fluids, which is well recognized as a prerequisite to the successful outcome of any major surgical operation, is especially necessary before prostatectomy. The skillful administration of water, plasma and saline and glucose solutions accordingly plays an important role in successful therapy;* the details of this aspect of the treatment of prostatism were presented by Simeone[1] in 1941.

Many of the less severe degrees of urinary infection can be allayed with the aid of a urinary antiseptic such as sulfadiazine. Of equal or greater value is the prevention of infection by avoiding, whenever possible, the use of the inlying urethral catheter, for the urethra is known to be a constant source of bacteria that rapidly increase in number and virulence owing to the inevitable trauma of an inlying catheter. Therefore, when drainage of the bladder for longer than a day or two before operation has been necessary, it has been the practice in this clinic to introduce a suprapubic catheter through a trocar or so-called "punch." This procedure causes no discomfort, and the bladder can easily be kept aseptic by the use of a closed system connecting the catheter with the drainage bottle. Austen's[2] report gives the details of the punch method of bladder drainage.

The most recent advances in prostatic surgery relate to the control of hemorrhage at operation and subsequently. This problem has long been found difficult, and many devices have been applied to its solution. Packing around an inlying catheter, ligation of bleeding points or coagulation by the high-frequency electric current and, especially in recent times, the pressure exerted by a distensible rubber bag (Pilcher) have been used with varying degrees of success. The packing and pressure-bag methods, even if efficient in controlling bleeding, almost always cause an extreme degree of vesical discomfort and tenesmus that makes the day or two after operation uncomfortable and requires heavy sedation. The electrocoagulation or actual ligation of bleeding vessels frequently fails to bring about really adequate hemostasis, because the actual bleeding points deep in the prostatic cavity are difficult to reach and identify.

The use of a coagulant that is normally a factor in the production of a blood clot — namely, thrombin — remains to be explored. Its action in converting soluble fibrinogen into insoluble fibrin can be considered the fundamental reaction in the coagulation of the blood.[3] Until recently, however, thrombin was difficult to isolate in a sufficiently concentrated form to be of value in producing a firm and adherent clot over a bleeding surface. Also, it is evident that some sort of matrix by which the thrombin can be prevented from being washed off in the blood stream is needed. Such a supporting substance has been found in fibrin in a form with many spongelike interstices that is called, for convenience, "fibrin foam."[4] Both thrombin and fibrin foam are but two of the many important results of the work of Cohn and his colleagues[5] in the Department of Physical Chemistry, Harvard Medical School, under contract between the Office of Scientific Research and Development and Harvard University, to study the fractionation products of human blood plasma. Without doubt the most exacting circumstances demanding hemostasis are those encountered in neurosurgery. In this field the investigations of Bailey and Ingraham[6] have shown the great value of the fibrin-foam method, in which the foam remains permanently in the tissues but is quite nonirritating and rather quickly absorbed.

The observations presented below, in which the foam method is applied to the prostatic cavity, do not concern the factors of absorption of the matrix. As a matter of fact, the foam has been found to be insoluble in urine.

METHOD

The solution of thrombin is made by dissolving the dry powder in about 10 cc. of an isotonic solu-

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tion of sodium chloride. In this solution pieces of foam about 1.5 to 2.0 cm. square are immersed and agitated until the air in the interstices is largely replaced by fluid. These pieces are then placed in the cavity of the prostate so as to fill it entirely, beginning at its apex and continuing to include the torn edge of the trigone (Fig. 1). Pressure is exerted over the mass of foam by a thin layer of surgical gauze, and the whole area is subjected to suction through a bent glass tube in the form of the usual perforated douche nozzle. Since the blood is thus drawn into the thrombin-soaked foam, coagulation takes place in about five minutes. Usually no additional hemostatic measure is needed. If a single vessel bleeds so sharply that control by foam and pressure is not possible, sparking by the high-frequency electric current should be employed. When such a rare arterial spurter is present, it is usually situated just under the torn edge of the trigone in an area readily accessible without removal of any of the foam already in place. Since occlusion of vessels by sparking, even though light, is accompanied by tissue necrosis, this method should be used only when unavoidable.

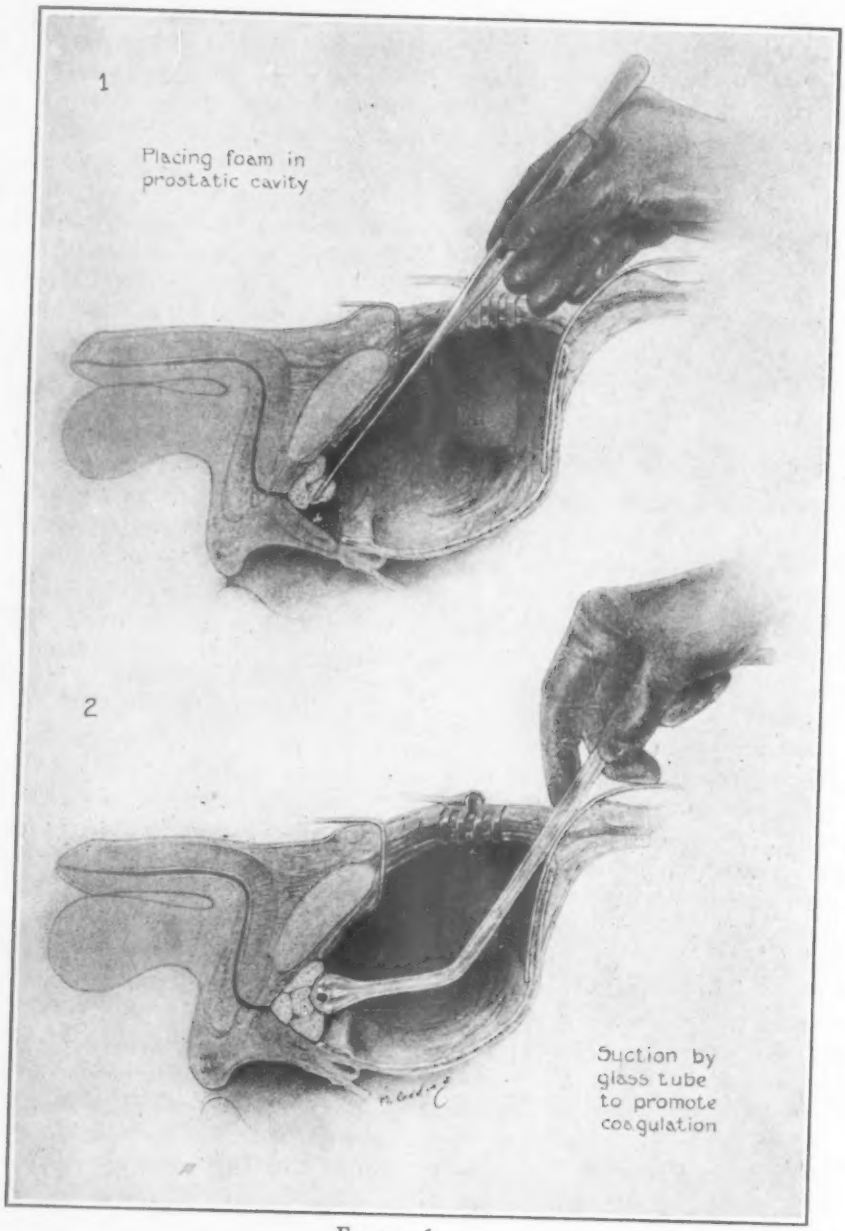

FIGURE 1.

Patience, continued pressure and suction are the essential factors in the production of hemostasis by this procedure. After complete hemostasis has been obtained the bladder is closed by interrupted sutures of fine catgut. A catheter with a mushroom end (Pezzer), of a size approximately No. 20 Fr., is ad-

justed in the upper angle of the wound for drainage of urine. The structures in front of the bladder are united by sutures of fine silk. After operation lavage of the bladder is avoided entirely; indeed, in the absence of bleeding and clot formation such irrigation has no place. The siphon effect of the suprapubic tube is sufficient to carry away the urine soon after it reaches the bladder from the kidneys. A "quiet" bladder, with no stimulus either to expand or to contract, results. This is a significant factor in prompt healing and a smooth early convalescence.

Following operation, fluids are forced to at least 3000 cc. daily. The patient is urged to get out of bed on the first postoperative day for a short period in both morning and afternoon. The suprapubic catheter is allowed to remain in place until about the third or fourth day, when the urine is again clear. Aided by the oblique route of insertion, abdominal pressure quickly closes the sinus tract after removal of the catheter, and spontaneous urination is resumed a day or two later. The foam is passed from the bladder in the form of small, slimy bits, without any suggestion of obstruction. If spontaneous urination seems delayed because of the foam, the single gentle passage of either a metal catheter or a sound serves to dislodge the foam. This passage, however, is rarely needed.

Results

In the most recent 88 consecutive cases of prostatic obstruction at the Peter Bent Brigham Hospital, 36 patients were treated by transurethral and 12 by perineal prostatectomy; the suprapubic route was employed in 40 cases, fibrin foam being used as a hemostatic agent.

The age of this last group of patients was as follows: fifty to sixty years, 8 cases; sixty to seventy years, 22 cases; and seventy to eighty years, 10 cases.

The smallest prostate gland weighed 20 gm., and the largest 107 gm., the average being 40 gm.

Preoperative drainage of the bladder was effected through a suprapubic punch in 6 cases and through a urethral catheter (for a short period) in 7; no preoperative drainage was performed in 27 cases.

The urine was clear on inspection two to four days after operation. The suprapubic drain was removed, on the average, slightly over five days after operation. The wound was healed and dry and voluntary urination had been resumed, on the average, eleven and a half days after operation. The reduction in the length of time from operation to resumption of voluntary urination — from fourteen and a half days in the first 10 cases to nine and a half days in the last 20 cases — is to be explained by increased experience regarding the interval after which bladder drainage could safely be abandoned.

Especially noteworthy is the fact that in no case was there any secondary bleeding. Lavage of the bladder was early abandoned, and the distinct impression was obtained that a bladder thus put at rest, without stimulus to its normal action of expansion and contraction, is an important factor in early healing of the injured area.

Summary

The method employed in the use of fibrin foam as a hemostatic agent after suprapubic prostatectomy is discussed, and the results obtained in 40 consecutive cases are described.

Since the above clinical observations were made, operations have been performed in several additional cases in which bovine thrombin in a matrix of gelatin (Gelfoam) was used instead of the human products. Hemostasis by these materials seemed as satisfactory as that produced by human fibrin and thrombin.[7]

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Discussion

Dr. John M. Fallon (Worcester): I am not competent to discuss Dr. Quinby's paper, but it has been suggested that I talk to you about the use of fibrin foam in general surgery, because these new fractions are, in my opinion, as important in clinical surgery as the older fraction — plasma — to which we are more accustomed.

Human blood fractions, supplied to the clinic through the kindness of Dr. Franc Ingraham by the Department of Physical Chemistry, Harvard Medical School, have been used one hundred and seventy-five times in 160 cases in general surgery. The fractions were thrombin, fibrin foam and Fraction 1 (fibrinogen), and the purpose of study was the development of applications in general surgery. I shall discuss only the combination of fibrin foam and thrombin that Dr. Quinby has described.

First, so far as the hemostasis of incisions into solid organs is concerned, the most useful application has been in thyroidectomy. Only the larger spurters need be clamped, with six to ten clamps on each lobe. These clamps are tied, and no second round of clamps is applied. The remnant of the thyroid gland is not sutured. Sheets of foam on the cut surface do the rest. The advantage consists not only in reduction of suture material but also in avoidance of trauma to the thyroid remnant. One may intend to leave a fifth or a sixth of the gland, but if such a fifth or sixth is full of sutures it may be physiologically a tenth. The suture that the foam supplants endangers the recurrent nerve crossing behind the gland. Foam has also successfully controlled oozing from incisions into the pancreas, liver and kidney.

Secondly, to obtain hemostasis on soft surfaces and in areolar spaces — spaces on which it is difficult to apply clamps, foam invariably succeeds. An especially rewarding application is to tissues distorted by disease and situated near vulnerable structures like the ureter, phrenic nerve and twelfth nerve, when the foam is substituted for blind clamping and deep sutures. The most frequent application in this group is to the subvesical veins, which are encountered in hysterectomy and in vaginal operations. The neck, the erectile tissues of the labia, the retroperitoneal spaces, the mesentery and the intestine are good examples of such soft areas.

Thirdly, control of direct hemorrhage of large vessels, which was attempted merely to show that it should not be

done, was not tried in human subjects. In eight operations on dogs, major arteries up to 4 mm. in diameter were either opened on the side or transected. With normal blood pressure, the arteries of 2 mm. and sometimes those of 3 mm. were controlled by foam and pressure. Some clots blew off when the blood pressure was artificially raised, but after the blood pressure had returned to normal, new applications of foam invariably held. Two arteries of 4 mm. could not be controlled by foam until the pressure had fallen to dangerous levels.

The use of foam is not recommended for openings into major vessels. In arteries there is the hazard of a large hydraulic pressure acting over a large area, and in veins the added risk of insucked thrombin, causing thrombosis elsewhere in the body. One of my colleagues, however, suddenly faced with a laceration of the vena cava in a patient in bad condition, successfully held a pad of foam over the opening by suturing peritoneum over it. This patient ultimately died from other causes, and autopsy showed neither hemorrhage in the area of the vena cava nor thrombosis elsewhere.

Fourthly, foam is employed as a filler of cavities. Foam is a stuffing that has hemostatic qualities and can be replaced by reparative tissues. Usually only a small amount is needed. Up to 25 cc. has been used, however, without visible ill effect. A dramatic application has been in the removal of Bartholin's cysts. Often the small artery at the upper end of the cyst escapes the clamps, retreats into the spongy paravaginal tissues and bleeds. Foam has ended all this. Wens, stripped varices and ganglions — that is, areas that can later be watched from the surface — when filled with foam have done well. And deeper, larger areas that cannot be watched, like the pararectal space, seem to have done well.

Fifthly, foam is used as a dressing. Following an accidental observation that better epithelium seemed to grow more quickly under foam, such dressings were used on several skin defects and in two defects of the mucosa (mouth and sigmoid), with good results. Foam, incidentally, is an excellent dressing for anal operations. At the end of an operation the anoscope can be reinserted to check what has been done without fear of stirring up hemorrhage if followed by a foam plug. Foam has also been used as an internal dressing, wrapped around intestinal anastomoses in dogs and in human beings, but it is not yet possible to report the results.

Complications include the danger of squeezing thrombin into a large vein. Two out of 160 patients had femoral thrombosis. This incidence is high, but the total group is small for conclusions. However unscientific it sounds, this was a group of patients picked from a larger total and containing most of those members of the total who were likely to have thrombosis.

Finally, blood fractions are neither an excuse for carelessness nor a substitute for good judgment, but the knowledge that blood fractions were available led me to attempt procedures that a few months previously would not have been considered. Amusingly, the fact that the foam was available has increased my respect for simple pressure. Often, by the time the foam reached the table, the bleeding had stopped; when foam was added, however, there was no fear that hemorrhage would occur.

DR. FRANC D. INGRAHAM (Boston): There is nothing for me to add to Doctor Quinby's paper or to Doctor Fallon's discussion. My experience has been chiefly with the use of the materials described in neurosurgical patients.

I should like to emphasize the facts that during the war all these materials were derived from Red Cross blood and that none of them were distributed to civilians except as testers for the armed forces. After the material had been released by the testing group, it was sent to the Army or the Navy.

TREATMENT OF MENTAL ILLNESS AT HOME BY SMALL DOSES OF INSULIN

An Appraisal of Results in Twelve Cases

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SINCE the introduction of insulin coma in the treatment of certain mental disorders by Manfred Sakel in 1933, the method has gained wide acceptance. The most extensive evaluation of the results with insulin coma is contained in a recent report of the New York Temporary Commission on State Hospital Problems,[1] which strongly favors insulin as being of definite value in the treatment of schizophrenia. This report is based on 1128 patients treated with insulin and on 876 control patients who did not receive any form of shock treatment. The former group had a definitely shorter period of hospitalization than the latter, as well as a longer period of satisfactory adjustment at home and a higher level of usefulness in the community. This type of therapy is drastic, however, and requires hospitalization, and there are a large group of patients whose mental condition does not require hospitalization. The purpose of this paper is to present experiences with a modified form of insulin-coma therapy in such patients at home.

The possibilities of insulin subcoma as a method of therapy have been only scantily explored. The first report of the therapeutic use of mild hypoglycemic shock was that of Cowie et al.,[2] who in 1923 noted that depressed states frequently cleared up during the insulin treatment of diabetes.

Subsequently, other reports suggested that such therapy might be beneficial. Among these is the work of Targowla and Lamache,[3] who in 1926 used insulin on 2 undernourished, depressed psychotic patients, and of Miskolczy,[4] who in 1927 worked with insulin in a variety of neurologic conditions.

In 1929 Appel and his associates[5] found insulin subcoma of value in improving the appetite and the nutritional and mental status of patients suffering from neurasthenia, depressive states and dementia praecox. The amount of food intake was increased in practically all cases, and the gastrointestinal function seemed to be improved. The dry, gray, flabby skin soon took on a healthy appearance. Not a few patients gained weight to an extent not previously experienced — a remarkable observation, since most of the patients were over forty-five years of age.

The first report on the prolonged therapeutic use of repeated mild hypoglycemic shocks over a long period in mental disorders was that of Polatin, Spotnitz and Wiesel[6] in 1940. Their group included

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18 patients with schizophrenia, manic-depressive psychosis and psychoneurosis and 4 with psychoses due to brain damage. The treatment consisted of daily hypodermic injections of small doses of insulin — initially 5 units, increased by 5 units daily to the point of mild hypoglycemia. The hypoglycemic symptoms usually began to manifest themselves about two hours after injection and gradually increased in severity. Patients remained in this state for from fifteen to forty-five minutes, depending on the degree of the hypoglycemia, which usually terminated with breakfast three or four hours after injection. During the hypoglycemia, the patients were up and about and were able to feed themselves at breakfast without assistance. They were treated daily for an indefinite period until improvement occurred. This ranged from one week to eighteen months. It was noted that most patients gained weight and that all became easier nursing and feeding problems. Of the 22 patients treated, 1 recovered, 12 were improved, 5 were slightly improved and 4 remained unimproved. No coma, allergic manifestations, convulsions or injuries occurred. These studies indicate that mild hypoglycemic shock is of considerable value in the treatment of mental disorders. The authors emphasize the fact that beneficial effects were slowly accumulative and that prolonged treatment was necessary before satisfactory results were observed. Subsequent reports of these authors[7, 8] in a large series of cases have confirmed their original impressions.

In 1940 Bennett and Miller[9] tried subshock doses of insulin in psychotic patients presenting difficulties in management. The treatment was given in 125 cases presenting extreme nursing problems, and nearly every case of acute manic excitement was controlled without sedatives within an average period of thirty-six hours after adequate insulin dosage. The use of sedatives was practically eliminated in cases of extreme psychomotor activity.

Ambulatory insulin therapy was utilized by Tomlinson and Ozarin[10] in 1942, according to the method described by Polatin and his co-workers. In a group of 52 unselected cases, 34 patients (65 per cent) improved, 5 (10 per cent) improved and then relapsed and 13 (25 per cent) showed no improvement. A year after this program had been initiated, 13 patients (25 per cent) had been paroled from the hospital. In dementia praecox, paranoid type, which comprised the largest number of cases treated, 60 per cent of patients were definitely improved. It is interesting that a patient with Alzheimer's disease improved and that 2 paretic patients showed a favorable response.

Rennie,[11] in 1943, reported 28 heterogeneous cases in which insulin in doses of 50 to 90 units daily over a period of twenty to fifty days gave especially gratifying results in the relief of excitement, overactivity, inner tension and, particularly, anxiety. Rennie found that insulin sedation was superior to sedation by ordinary chemical methods, the effects being more incisive and lasting. It was apparent that dramatic relief could be achieved with insulin in various kinds of excitement whenever anxiety prevailed. Insulin therapy permitted a marked degree of relaxation, released ability to discuss preoccupations easily and provided the therapist with a real opportunity to understand the patient and his basic needs.

Beneficial results with subcoma insulin have been reported in the treatment of acute alcoholism[12] and the relief of severe migraine headaches[13] and as an aid in rehabilitating soldiers suffering from acute panic, protracted states of anxiety and chronic weight loss.[14, 15]

A recent report by Sands,[16] summarizing his experiences in 163 cases, advocated subcoma insulin in the treatment of war neuroses.

Referring to insulin subcoma treatment of ambulatory patients, Brickner[17] states that the method is extremely useful in the relief of tension associated with practically every type of mental or emotional disturbance.

The following report deals with the results of prolonged subcoma insulin treatment in a consecutive series of 12 ambulatory patients with chronic mental illness that had been refractory to other forms of management.

Method

Breakfast is withheld each morning. Insulin injections are given six times a week in increasing amounts until mild hypoglycemic shock, manifested by weakness, copious perspiration, hunger and drowsiness, is produced. Usually 50 to 90 units is a sufficient dosage. When mild hypoglycemic shock occurs, the dosage is maintained at the same level so long as the optimum effect continues. In some cases, however, the dosage must be further increased.

Mild coma occasionally supervenes, but the patient is deliberately prevented from going into deep coma. Generally it is observed that after several weeks of continued insulin therapy, the patient develops a certain amount of sensitivity to insulin, and thereafter it is possible to obtain reactions with a reduced dosage. The insulin dosage is at all times kept at a minimal level, and the intensity of the hypoglycemia is controlled by feeding. In this way, patients feel more comfortable, whereas with larger doses they are apt to express feelings of discomfort and even to suffer from nausea and other gastrointestinal manifestations.

As a rule the hypoglycemic manifestations appear in approximately an hour. If insulin is injected intravenously the symptoms usually appear in an appreciably shorter period. Generally the patient is quite comfortable during the first half hour, although there are individual variations.

Experience shows that frequent modifications and variations are often essential for the success of this

method. During the treatment patients are up and about, but, if they prefer to lie down when the hypoglycemic manifestations become upsetting, they are permitted to do so.

It is advisable that the patient be kept under constant observation by the physician or a trained nurse, and that the pulse, blood pressure, respiration and general clinical status be checked at frequent intervals. Those in attendance are instructed regarding the complications that may arise and their management. Barbiturates are contraindicated during the insulin series, since they may negate the effect of the insulin.

The patient is permitted to remain in a state of mild hypoglycemic shock for a variable length of time, and termination is then brought about as described above. In the early phases of hypoglycemia, psychotherapeutic discussions are carried out.

The results of the method of therapy in the following 12 cases appear to justify its continued use.

CASE 1. A 28-year-old married Italian immigrant who had suffered considerable early privation in his native land came to America at the age of 17 and successfully operated a barber shop until November, 1943, when in response to wartime stress he developed marked tension, restlessness, anxiety and obsessive fears, the most prominent among which was worry that he would slit the throat of his customers while shaving them. This led to a marked inefficiency and almost complete incapacity in his work. He complained of weakness, pain, dizziness, insomnia, anorexia, tremors and temper outbursts.

Insulin subshock was begun on January 28, 1945. Improvement was first noted on February 26, and thereafter there was a gradual abatement of all symptoms until complete recovery on May 13.

The patient was entirely well at follow-up examination 8 months later.

CASE 2. A 30-year-old married Italian woman with a history of attacks of depression at the ages of 16 and 26, succumbed to a third depressive psychosis in March, 1944, following her husband's entry into the armed forces.

The symptoms consisted of insomnia, numerous somatic complaints, worry, fatigue, spells of weeping and obsessive longing for her husband. The illness continued for a year, and the patient lost a total of 39 pounds in weight.

She made a suicidal attempt by swallowing iodine. Neither hospitalization nor electric shock treatments were permitted. The constant threat of suicide made the situation desperate.

On March 17, 1945, insulin subcoma treatment was begun, and the patient made a dramatic improvement in 5 weeks. In 12 weeks she had regained 23 pounds in weight. She was cheerful, interested, self-reliant and confident about the future. Recovery persisted.

CASE 3. A 40-year-old married woman, whose family history revealed suicide of one parent and whose early life had been essentially normal, first developed symptoms in 1941 following an attack of influenza. She showed the typical reactions of a shut-in personality. Tension, nervousness and obsessive fears persisted for months, resulting in marked incapacity. There was a sense of impending disaster, as well as various somatic complaints. Extreme emotional instability — characterized by laughing and crying spells, agitation and panic reactions — resulted in a state of utter helplessness. This condition remained unabated except for short periods of relief during the summer months.

Prolonged treatment with barbiturates and other drugs was unsuccessful. Orthodox psychotherapy by several competent psychiatrists, as well as several years of psychoanalysis, was of no avail in alleviating the symptoms. Electric-shock therapy was equally unsuccessful, except for a brief period of partial relief of symptoms. An exhaustive medical examination failed to reveal any evidence of organic disease.

In May, 1945, insulin therapy was initiated, beginning with a dose of 10 units and increasing the dosage daily until symptoms of mild hypoglycemic shock were present. Sixty treatments in all were given, the maximum dose being 90 units.

After 5 weeks of treatment, there was a gradual and remarkable remission of the symptoms. Tension and anxiety diminished, the weight increased steadily and the patient was able to resume social activities and derived considerable pleasure and satisfaction out of life. She became more accessible to psychotherapy, and improvement continued steadily until complete recovery 10 weeks after the initiation of the therapy.

The patient subsequently remained well, and for the first time in 5 years was not confined to bed during the winter.

CASE 4. A 56-year-old married man with a noncontributory family history had suffered for 6 years from pain in the post-thoracic region radiating laterally. A diagnosis could not be established despite the concerted efforts of many specialists. Novocain nerve-root injections were given, but after 3 weeks of comparative comfort the pain returned.

The patient suffered for 8 months, during which x-ray treatment of the spine gave temporary relief. Exercises and diathermy given by an osteopath aggravated the pain. Opiates gave partial amelioration during hospitalization. After a second novocain injection the patient collapsed completely and had to remain in bed for several days.

A depression followed. The symptoms consisted of despondency, loss of weight and poor appetite. No response was obtained to sedatives.

At a private sanatorium a course of electric shock treatments brought some palliation for 9 months, but in February, 1945, the patient relapsed into depression. Various forms of medical management proved ineffective. The patient had crying spells and suffered from anhedonia, insomnia, inability to concentrate, a host of bodily symptoms and extreme anxiety.

Insulin subshock treatment was begun on May 11. The response was most encouraging; the patient began to gain weight, the appetite improved and he was able to work and showed renewed and sustained interest. He was treated until August 27, when he felt well enough to take a vacation for a week. Improvement lasted until October 9, when the patient reacted to slight external stress by becoming mildly depressed.

He continued to receive additional treatment intermittently, during which his condition fluctuated. For an occasional day or so he slept poorly and complained of headaches and vague pains. In general, however, his condition remained satisfactory. He was able to attend to his business duties, which he had not been able to do satisfactorily before treatment. The depression largely abated, and the patient gained weight and appeared well.

CASE 5. A 37-year-old, overprotected, married Italian woman, with a history of nervousness in childhood and difficulty in adjustment in play life, first succumbed to any clearly defined illness in the post-partum period of her first delivery. She developed weakness, apathy, loneliness and seclusiveness. Two years previously, following the death of her mother, she had been depressed for 4 months.

In June, 1945, she suffered an acute turmoil reaction characterized by irritability, mood swings, agitation, delusions and hallucinations. No effect was obtained by a variety of medication or by a change of environment.

Insulin subshock treatment was immediately begun, and in 2 weeks the symptoms began to clear. A total of 92 subshock treatments were necessary to restore the patient to mental health.

She was well when last seen.

CASE 6. A 26-year-old married man had been insecure, inadequate, emotionally unstable, suspicious and distrustful since the loss of his parents at an early age. He constantly complained of somatic disease, lack of energy and fatigue and indulged in self-reproach. His mood was chronically depressed.

Insulin subshock treatment was begun on June 30, 1945, and in a month the patient was able to handle his anxiety more adequately. His emotional life reached an even keel and his outbursts became infrequent. Treatment was continued with some interruptions until September 15. The pa-

tient was considerably improved but not completely relaxed. Further treatment was omitted, however.

The patient was mentally recovered at follow-up examination 6 months later.

CASE 7. A 42-year-old spinster became seriously ill in 1931 following a clandestine affair with a married man interested only in exploiting her. Suffering from anorexia and vomiting, she gave up her job and retired to a life of invalidism. She gradually sank into a state of tiredness, lassitude, self-depreciation, seclusiveness and emotional instability. Regurgitation and vomiting followed any suggestion of social intercourse.

Despite numerous attempts at medical management and psychotherapy, the condition continued unabated for 14 years — the only significant change being that the patient became more depressed and despondent. Since the family refused permission for electric-shock treatment and frowned on hospitalization, insulin subcoma treatment at home was begun on July 18, 1945, and continued for 4½ months.

The first short period of improvement was noted in 6 weeks. Thereafter, intervals of well-being became more prolonged. Psychotherapeutic sessions were soon possible with a patient who had previously been inaccessible. Hope and confidence came into the life of a woman who had been mentally ill for 14 years. The patient returned to work, and social adjustment was excellent.

CASE 8. A 40-year-old married woman, whose mother had been neurotic and whose father had been alcoholic, had led a gay, cheerful and useful life until a cesarean section in 1942 resulted in a dead infant. Both the patient and her husband were deeply grieved over the loss, with intensification of dissatisfaction and yearning when future months left them barren and childless. The patient began to blame herself and expressed feelings of guilt over past sexual indiscretions and excessive concern over a brother's neuropathic tendencies. This condition continued intermittently until 1943, when she became seriously depressed and was treated with electric shock, which gave only temporary relief.

In June, 1945, the patient presented a picture of anxiety, somatic disturbances, marked phobias and a fear of death oscillating with periods of gaiety and euphoria. Insulin subcoma treatment was begun in August, and continued for 4 months, the patient receiving a total of ninety-six treatments. Ten weeks of treatment resulted in loss of anxiety and of feelings of guilt. She gradually became more objective, contented, active and stable in her adjustment to her environment.

Follow-up study 4 months later revealed that the patient had not lost any of the gains made under insulin subcoma treatment.

CASE 9. A 46-year-old, married, artistic woman, overwhelmed by the shock of several deaths in her family and a serious heart ailment in her husband, succumbed in 1944 to an illness marked by fatigue, anxiety, gastric distress and abhorrence for food and water. Financial difficulties, more bereavements and an increasing feeling of loneliness seemed insuperable obstacles to recovery. Of psychologic interest was the fact that on several occasions news of a death in the family came at the time the patient was eating a meal; avoidance of food and drink was the result of this conditioning. Amenorrhea of 6 months' duration developed; the patient took to barbiturates, with indulgence to levels of mild toxicity.

Insulin subshock treatment was begun on August 21, 1945. Improvement was noted in 1 month, the patient slept well without medication and actually experienced pleasurable sensations of hunger and thirst without distress at their satisfaction. At the end of fifty treatments she had gained 12 pounds in weight. Curiously, she showed little enthusiasm for her recovery and weight gain and a reluctance to continue with the therapy, which was soon discontinued.

Follow-up after 5 months revealed that patient had slipped slightly and returned to her former weight level, but as she was no longer a barbiturate addict, she could engage with interest and enjoyment in art, and seems to have partially maintained her improvement.

CASE 10. A 47-year-old married man became ill in 1942, when he suspected his wife of a clandestine love affair. The symptoms consisted of insomnia, worry, crying spells, inability to concentrate, loss of interest and spontaneity. He hired detectives to trail his wife and contemplated divorce. In May, 1944, he had an attack of coronary thrombosis. This preyed on his mind and added to the already heavy strain. He constantly chided his wife for his mental state and cardiac disease. During a vacation trip to Florida he was unable to eat or sleep and paced the floor at night, repeatedly accusing his wife, with resulting tension, discord, unrest and bitterness. The distress was not relieved by barbiturates, health resorts, osteopathic treatments and therapy from competent internists and psychiatrists.

Insulin subshock treatment was begun in October, 1945, after assurance by medical specialists that the patient was a good risk. On November 19, a definite upturn was noted. He lost considerable anxiety and gradually became more amenable to psychotherapy. He was able to see his mental problem in a new light.

The remission lasted until February, 1946, when the patient was again beset by doubts, fears and obsessions, which were of short duration, however. As treatment was continued his anxiety completely disappeared, he became jovial and interested in life and resumed the operation of a large and successful business. A total of one hundred and two subshock treatments completed the series.

The excellent home and business adjustment continued.

CASE 11. Following a series of abdominal operations and a loss of 30 pounds in weight, a 38-year-old married woman, whose personality was characterized by egocentricity, selfishness and excessive self-esteem, became embarrassed and self-conscious, lacked interest, ambition and spontaneity and showed excessive irritability when crossed. She complained of fatigue and headaches. The patient took refuge in barbiturates and suffered from mild barbiturate addiction.

Insulin subcoma treatment was begun in November, 1945, and definite improvement was experienced starting with the eighth treatment. Progressively there was a return of appetite and sense of well-being and a gain of 12 pounds in weight. The patient was more relaxed and showed no anxiety or irritability.

After the forty-sixth treatment insulin subcoma was omitted because of a death in the family. Thereafter the patient refused to co-operate for further treatment, stating that the therapy was too restraining and interfered with her social life.

Loss of weight, insomnia, return of irritability and barbiturate addiction followed the cessation of treatment.

CASE 12. The whole life pattern of a 23-year-old man had been characterized by marked inadequacy, self-consciousness, immaturity, lack of drive, initiative or sustained interest, and excessive sensitivity to criticism and rebuke. He broke down in 1939 following the loss of a Government job and consequent severe disappointment in his future. He became more dependent and resentful of others and displayed outbursts of temper. In 1945, examination revealed an introverted, weak-looking man, who was lacking in confidence and complained of poor appetite and insomnia. He had been socially maladjusted, with low spirits, had had frequent crying spells and had not evinced the slightest interest in girls.

Following one interview, conducted under sodium amytal, insulin subcoma treatment was begun in December, 1945. A slight improvement was noted 5 weeks later. The patient gained 10 pounds but was still shaky, unstable and resentful toward his parents. Improvement with further treatment was steadily progressive. Ten weeks after treatment was begun the patient was eating and sleeping well and had gained confidence and poise, and his spirits had risen.

Insulin subcoma treatment has proved valuable in a variety of mental conditions and in many cases that have been refractory to other methods of management.

This treatment has the following advantages: it can be administered in the patient's home and thus obviates the stigma (in the minds of the patient and his relatives) of hospitalization—none of the current drastic methods (electric-shock treatment, insulin-shock treatment and lobotomy)

can be applied readily at home; the method is relatively safe when administered by well trained personnel who are in constant attendance during the period of treatment; the aftercare is rather simple and imposes no undue hardship on either the patient or those in attendance; insulin subcoma is less drastic than actual shock treatment and in all probability produces no irreversible brain damage (patients given as many as one hundred and two subcoma treatments showed no evidence of mental deterioration); the treatment, which is not incapacitating and during which the patient is more or less conscious and usually able to be up and about, has two important advantages over other methods — first, the patient can participate in the psychotherapy, can speak freely of his preoccupations and experiences and can better unburden himself of his distressing thoughts, enabling the therapist to obtain a closer understanding of the patient and his basic needs, and secondly, at the termination of the treatment, the patient is alert and able to join in activities immediately and is not in the toxic, beclouded state characteristic of electric-shock treatment, insulin-coma treatment or heavy barbiturate medication; insulin subcoma greatly relieves basic anxiety — according to Rennie[11] the improvement appears to run parallel with the disappearance of dynamic anxiety; although the period of treatment is more prolonged than that in the more drastic types of therapy, the beneficial effects are usually quickly apparent and cumulative; and finally, the effects of subcoma insulin treatment are more incisive and lasting than those with chemical sedation,[11] which often increases anxiety rather than relieving it.

Chemical methods (interviews conducted under sodium amytal) are apt to be rejected by the patient as an aggressive attempt to elicit painful memories that he would prefer to remain hidden.

The period of follow-up study in the cases reported above varied between four and nine months. The final evaluation of this method of therapy must await a longer study of all these cases, as well as a careful investigation of a larger series of cases. The results, however, even in the short period of observation, were quite encouraging and support the findings of Rennie, Brickner, Polatin and others.

Subcoma insulin treatment seems to have almost a specific effect in relieving anxiety and tension. The role that anxiety and tension plays in misinterpretations, delusions and depressions can hardly be overestimated.

A natural disadvantage of this type of treatment in the patient's home is the time factor, several hours of the physician's attention usually being required. With this precaution, the treatment is relatively safe. It is emphasized that insulin subshock treatment must not be given promiscuously and haphazardly.

Summary

Subcoma (mild hypoglycemic) shock therapy can be administered at home to ambulatory patients with comparative safety. Twelve cases are reported, with results that appear to justify further use of the treatment. The method of administration and the necessary precautions to safeguard the patient are described.

The advantages of repeated subcoma insulin shock treatment are enumerated. Weight gain and increased sense of well-being are important concomitants.

Patients with varying neuropsychiatric conditions, some of which were refractory to other methods of management, showed dramatic improvement or recovery. The beclouded, toxic state regularly encountered with the more drastic types of therapy, such as electric shock and insulin coma, is largely eliminated.

In view of the favorable results encountered and the hopeful reports in the literature, further use of this method is believed to be warranted.

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THE SIGNIFICANCE OF MEDIASTINAL EMPHYSEMA*

A Report of Two Cases

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SPONTANEOUS mediastinal emphysema is now a well recognized clinical entity to which considerable attention has been called. Although Hamman[1] enumerated several routes by which air reaches the mediastinum, the finding of extensive mediastinal and subcutaneous emphysema may at times be too readily attributed to this relatively benign disorder and a serious underlying disease overlooked. It is the purpose of this paper to call attention to that possibility by presenting 2 cases. In Case 1 spontaneous mediastinal emphysema occurred twice, and at the time of recurrence mediastinal decompression became necessary. In Case 2 extensive mediastinal and subcutaneous emphysema was dependent on a serious underlying disorder, discovered at autopsy to be spontaneous rupture of the esophagus. Some points of similarity and the differential diagnosis of the two conditions are discussed below.

Case 1. I. B., a 19-year-old girl, entered the hospital because of severe substernal pain and dyspnea. She had been well until 3 days before entry, when she had noted a head cold. Eight hours before admission she suddenly began to cough and vomited. She felt ill and went to bed, where 15 minutes later she experienced a sudden violent pain over the xiphoid process radiating through to the back but not to the shoulders or arms. The pain was accompanied by severe dyspnea and orthopnea and was aggravated by coughing, by deep breathing, and by lying on the right side. The pain continued undiminished until the time of entry.

Physical examination revealed a well developed, well nourished girl who appeared to be acutely ill and in respiratory distress and who was breathing shallowly and regularly. The temperature was 100.2°F., the pulse 108, and the respirations 30. The blood pressure was 130/95, falling to 110/70 about 4 hours later. Crepitus was felt over the face, the occiput, the entire neck and the upper anterior chest. The trachea was deviated slightly to the right. The left side of the chest was hyperresonant, with diminished breath sounds. The area of cardiac dullness was obliterated. The heart sounds were distant; no abnormal sounds were heard. Percussion over the liver revealed dullness. There was no cyanosis or venous engorgement. The remainder of the examination was not remarkable.

The urine was normal. Examination of the blood revealed a hemoglobin content of 80 per cent, and a white-cell count of 14,000, which fell to 6350 on the 2nd hospital day. A blood Hinton test was negative, and a blood culture yielded no growth. A chest roentgenogram, showing a fine line of decreased density to the left of the sternal border that extended down the sternal border and about the pericardium, was regarded as consistent with mediastinal emphysema; there was no pneumothorax. An electrocardiogram was within normal limits.

The patient was placed in bed and given intranasal oxygen, a tight chest binder, codeine and aspirin and sulfamerazine. She was fairly comfortable, showing gradual symptomatic and objective improvement, but continuing to run a slight temperature. On the 2nd hospital day muffled crackling or crunching sounds synchronous with systole were heard over the apex of the heart, disappearing within a few hours.

On the 4th hospital day, while the patient was lying quietly in bed and not coughing, she had a sudden recurrence of severe pain and shortly became cyanotic, dyspneic and irrational. Bilateral subconjunctival hemorrhages appeared. Morphine did not control the pain, and oxygen administered with the aid of a Boothby mask gave no relief. The respirations rose to 40, the pulse to 140, and the blood pressure to 160/120. Crepitation reappeared over the face, but auscultation of the heart and lungs revealed no abnormality.

The patient was transferred to the operating room, where a 7.6 cm., low-collar incision just above the sternal notch was made under local anesthesia. The muscles were separated in the midline, and a finger was inserted into the superior mediastinum through the suprasternal notch. There was an egress of air, and rapid improvement in the status of the patient followed. The subcutaneous emphysema disappeared gradually, and convalescence was uneventful.

Case 2. C. M., a 58-year-old married man, entered the hospital complaining of abdominal and chest pain of 6 hours' duration. He had consumed considerable quantities of alcohol daily for many years, but he had remained well until 6 hours before hospital admission, when, shortly after carrying a heavy load of brass, he suddenly vomited copious amounts of brown liquid material; there had been no previous nausea. He continued to retch for 5 minutes. He noted marked weakness and shortness of breath, and experienced a severe pain in the anterior and posterior chest and in the upper abdomen; the pain was made worse by deep breathing. After going to bed the patient felt less dyspneic but observed that he was hoarse. Thereafter he noted that his neck was swollen. He had two more episodes of vomiting before entry. He had never had jaundice, ascites or ankle edema. The appetite had been poor, but there had been no dysphagia. No other contributory information was elicited.

On physical examination the patient was obese, flushed and in respiratory distress. The temperature was 101°F., the pulse 104, and the respirations 32. The blood pressure was 110/66. On palpation there was crepitus over the mandible, the entire neck and the anterior chest to the costal margin. The trachea was in the midline. There were prominent superficial veins over the right anterior chest. The anteroposterior diameter of the chest was increased. Tactile fremitus and resonance were decreased over the left lower lobe, and the breath sounds were faint. No rales were heard. The remainder of the chest was hyperresonant. The area of cardiac dullness was obliterated, but this finding was difficult to evaluate because of the emphysematous chest. The heart sounds were faint, and no murmurs were heard. Except for slight upper abdominal tenderness, there were no noteworthy physical findings.

No abnormality of the urine was noted. Examination of the blood revealed a hemoglobin of 80 per cent and a white-cell count of 3450, which rose to 15,200 on the 2nd hospital day. Examination of the sputum revealed no tubercle bacilli. The vomitus and a stool were guaiac negative. The blood Hinton reaction was equivocal. The venous pressure in the antecubital fossa was equivalent to 150 cm. of water, and the arm-to-lung circulation time, which was tested with paraldehyde, was 15 seconds. Roentgenograms of the chest and of the neck were regarded as consistent with mediastinal and subcutaneous emphysema. An abdominal film was within normal limits. An electrocardiogram showed sinus tachycardia, with slightly low origins of the ST segments in Leads 2 and 4.

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On bed rest the temperature quickly returned to normal and the dyspnea disappeared. In the hope of hastening resorption of air from the mediastinum, oxygen therapy was instituted.

About 14 hours after entry the patient again became dyspneic and the blood pressure fell to 80/40, where it remained until shortly before death. On the 2nd hospital day crepitant rales were heard at the lung bases. Because of the rales and the elevated white-cell count, although the temperature was normal, sulfapyrazine was given in full doses orally. A roentgenogram of the chest was interpreted as showing atelectasis of the right and left lower lobes. Later in the day the patient became violent, tearing away his oxygen mask repeatedly. The pulse rose to 130 and was of small amplitude. Dyspnea followed by cyanosis ensued, and since the signs of mediastinal emphysema were still marked it was believed that the only therapeutic measure with a reasonable chance of success was mediastinal decompression.

The patient was removed to the operating room where the superior mediastinum was entered digitally after a low collar incision had been made. There was some egress of air; cultures of the mediastinum were made, and the wound was closed about a rubber dam. For about an hour the patient appeared to breathe more easily and to be making slight improvement. Despite supportive measures, however, he slowly weakened and died 9 hours after operation and 48 hours after the onset of symptoms.

Autopsy. At post-mortem examination subcutaneous and mediastinal emphysema was found as clinically described. The essential abnormality was a longitudinal linear rupture of the esophagus, 2 cm. long, just above the esophageal hiatus of the diaphragm. It communicated with a cavity containing foul, dark-brown fluid, which bulged against the posterior aspect of the pericardium and was walled off from the left pleural cavity by fibrinous adhesions. Microscopically there was no evidence of peptic ulceration of the esophagus. Gas-forming bacilli were not found in the swabs taken from the chest at operation or at autopsy, although suitable procedures for culture were carried out. Additional findings were bilateral pleuritis due to a Type 5 pneumococcus, congestion and edema of the lungs, with bronchopneumonia, and moderate alcoholic cirrhosis of the liver. Death was attributed to respiratory embarrassment.

The pathogenesis, pathological physiology, clinical manifestations, diagnosis and treatment of mediastinal emphysema have recently been reviewed by Hamman,[1] who indicates the need for mediastinal decompression when signs of high pressure within the mediastinum manifest themselves, although in the absence of these signs rest and symptomatic measures suffice. Hamman lists four possible routes along which air may reach the mediastinum: through the fascial planes of the neck; through a perforation of the trachea, bronchus or esophagus; from the retroperitoneal space; and from the interstitial tissues of the lung. The entrance of air into the mediastinum via the second route rarely occurs, but Hamman further states:

> No doubt at times air may enter the mediastinum through a perforation of the esophagus. However, where this accident occurs there is always infection and the serious symptoms of infection obscure the lesser symptoms that may arise from a small amount of air entering the mediastinum.

This statement seems somewhat at variance with the findings in Case 2; indeed, McWeeny[2] described emphysema as one of the most striking and constant findings in spontaneous rupture of the esophagus. Ridgway and Duncan,[3] in a review of the literature, found emphysema present in a half to two thirds of the cases.

Case 1 provides an example of uncomplicated mediastinal emphysema, although it may be questioned whether it should be classified as an example of spontaneous mediastinal emphysema (Hamman's syndrome) or whether it should be excluded from the spontaneous type on the basis that fifteen minutes or more prior to the onset of pain the patient had experienced increased intrathoracic pressure associated with coughing and vomiting. The recurrence was known to have happened without any unusual exertion while the patient was in bed in the hospital. Thus it was clearly spontaneous. Regardless of classification this case illustrates the dramatic improvement that occurs with decompression of the mediastinum when the tension within the mediastinum is so great as to embarrass the circulation.

Case 2, which to those in attendance simulated Case 1, was nonetheless clearly one of spontaneous rupture of the esophagus. The findings were typical of the classic descriptions of the condition,[2, 3] the patient being a man, in middle life and alcoholic. Vomiting and retching immediately preceded the illness, which was characterized by a sudden onset, pain in the lower chest and upper abdomen, and shock, with dyspnea and subcutaneous emphysema. Spontaneous mediastinal emphysema, however, occurs in both sexes, alcoholism is not a factor and the condition arises without apparent precipitating factors. In spontaneous rupture of the esophagus—the term "spontaneous" being used rather loosely, but serving to exclude external trauma—violent retching and vomiting, often following the ingestion of an extraordinarily large meal, usually precede the attack. Both emphysema and esophageal rupture have a sudden onset, pain in the former being restricted to the chest, but in the latter, upper abdominal pain, sometimes with a boardlike abdomen, is found in addition to the chest pain. The pain in both syndromes may be aggravated by breathing, but marked thirst and shock are suggestive of esophageal rupture. The extent of emphysema is not of aid in the differential diagnosis; in fact, after esophageal rupture, it has been observed to involve the whole body. Aspiration of the chest through a needle may clinch the diagnosis by revealing the presence of gastric juice or food particles.

The course of spontaneous mediastinal emphysema is usually benign, but, as Hamman states, prompt decompression of the mediastinum may prove life-saving if the venous return to the heart becomes seriously impeded. In contrast, early intervention in spontaneous rupture of the esophagus seems mandatory, although closed drainage of the pleural cavity,[4] with chemotherapy, may be the procedure of choice.

A few additional points regarding spontaneous rupture of the esophagus may be of interest. This syndrome appears to bear a considerable relation to that described by Mallory and Weiss,[5, 6] in which

laceration of the cardia of the stomach occurs, with subsequent hemorrhage into the gastrointestinal tract. This occurs in heavy drinkers, usually following vomiting. It seems of interest that when the laceration results in esophageal rupture frank bleeding seldom occurs, especially in view of the observation that bleeding occurs in 29 to 53 per cent of cases of perforation of esophageal peptic ulcers.[7] Finally, mediastinal emphysema is not a prominent feature of perforation of esophageal ulcers, although it is one of the most striking findings in rupture of the esophagus.

Summary

Although mediastinal emphysema is usually spontaneous in origin and benign in its course, even the spontaneous variety may lead to serious circulatory embarrassment. Furthermore, the syndrome may be a prominent sign of a more serious underlying disorder. As illustrations, 2 cases are presented. One required mediastinal decompression because of a severe spontaneous recurrence of mediastinal emphysema. In the other mediastinal emphysema was but a sign of a different and more serious disease, which at autopsy proved to be spontaneous rupture of the esophagus.

The operations in both cases were performed on the Second Surgical Service, Boston City Hospital, under the direction of Dr. John W. Strieder, to whom we are indebted for cooperation.

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MEDICAL PROGRESS

ACUTE PULMONARY EDEMA, WITH SPECIAL REFERENCE TO EXPERIMENTAL STUDIES (Concluded)*

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BALTIMORE

Experimental Acute Pulmonary Edema

Experimental means of causing pulmonary edema are classified according to the general technic used.

Mechanical Methods

Welch,[74] in a large series of experiments in 1878, produced pulmonary edema experimentally by compression of the left ventricle or auricle and by ligature of the thoracic aorta. In spite of the grossness of this experiment and the many changes involved in such extensive manipulation, the conclusions of Welch remain as the cornerstone of the mechanical theory of pulmonary edema. Welch stated his conception of the cause as follows, "A disproportion between the working power of the left ventricle and of the right ventricle of such character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart."

The mechanical concept was supported by the findings of the German School.[29] It is obvious that high ligature of the aorta also cuts off the blood supply to the brain, causes cephalic hypertension if the ligature is beyond the left subclavian artery, and leads to dilatation of the heart and aorta. Thus, many other factors besides the mechanical one of obstruction to left ventricular output are involved in this experiment. It is interesting to note that Lichtheim and Cohnheim could not produce acute pulmonary edema by ligature of the aorta below the diaphragm or by ligature of all the pulmonary veins. Other workers were unable to repeat Welch's findings. These are important defects in the experiments.

Teisser, Guinard, and Arloing[29] could not produce pulmonary edema in curarized dogs, under artificial respiration with the chest open, by compression of the aorta, even though the pulmonary pressure rose two or three times.

In 1914 Modrakowski[19] made the interesting observation on mechanical forces that by means of high arterial pressure alone it was not possible to produce edema in the isolated, artificially circulated cat lung. Pressures up to 75 and 82 mm. of mercury were investigated.

Cataldi,[75] in 1935, sought to damage selectively either the right or the left ventricle by injections into the myocardium of silver nitrate and found, much to his surprise, that on damage to the right

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ventricle, two thirds of the animals developed pulmonary edema, whereas after damage to the left ventricle in a similar fashion he usually obtained fibrillation and only rarely pulmonary edema. This experiment certainly does not support the theory that left ventricular failure causes edema. Cataldi,[75] Luisada[27] and Rubino[76] decried the concept of partial insufficiency and demonstrated pulmonary edema following damage to either ventricle and to all parts of the coronary circulation.

In refutation of many of the conclusions drawn from mechanical production of pulmonary edema is the work of Antoniazzi as reported by Luisada,[27] a summary of which follows. Antoniazzi, following the classic method, found in fifty consecutive experiments in rabbits with an open thorax that ligation of the arch of the aorta or of three quarters of the pulmonary veins or the pinching and the crushing of the left auricle did not cause pulmonary edema. He considered opening of the chest to have some sort of negative influence and adopted a new technic in which he ligated the aorta without opening the thorax. With this method pulmonary edema appeared in all the experiments. To investigate the failure of pulmonary edema to appear in animals with an open chest, Antoniazzi made further studies, which revealed that edema appeared after ligation of the aorta with the thorax closed, even when oxygen was continuously injected into the trachea under elevated pressure; edema also appeared when the lungs were rhythmically ventilated from the trachea with an artificial respiration apparatus. Edema did not occur with the thorax open, even when the pleural cavity was subjected to a negative pressure and the lungs were ventilated by means of rhythmical decompression of the pleural cavity, reproducing the mechanical features of a closed thorax. It appears that pulmonary edema following ligation of the aorta is not due simply to the pulmonary hypertension; it does not occur if one opens the thorax — even if, with the thorax open, one places the lungs and pulmonary vessels in the hemodynamic or pneumodynamic conditions characteristic of a closed thorax. Stimulation of the pleura apparently inhibits in some way the onset of edema. That this is not a reflex was demonstrated by incision of the nerves to the lungs, a procedure that should block the efferent side of a protective reflex, which still did not cause edema. It is therefore suggested that pleural stimulation alters the activity of the nervous center in such a way that edema does not occur. Thus, any afferent impulses from the heart and aorta meet inhibition in the center and are unable to elicit efferent impulses capable of causing pulmonary edema. The peritoneum is capable of inhibiting the center, and opening of the peritoneum also prevents edema of aortic ligation. Certainly opening of the abdomen cannot alter the hemodynamics of the heart and lungs to any great extent.

If 5 cc. per kilogram of body weight of a mixture of narcotics (morphine 1:100, papaverine 1:1000 and chloretone 4:1000) is injected into an animal and the aorta is ligated with the thorax closed, pulmonary edema does not occur. Similarly if the stellate ganglions are removed bilaterally and the aorta ligated, no pulmonary edema ensues.

An explanation for these phenomena is that when the thorax is closed and the aorta ligated, cephalic hypertension and myocardial activity soon initiate a series of stimuli that arise from the myocardium, the coronary vessels, the arch of the aorta, the carotid sinus and the cerebral vessels. Such stimuli, going to the center, give origin reflexly to efferent stimuli to the pulmonary vessels determining pulmonary edema. It is possible to prevent this by three methods: pharmacologic depression of central excitability; depression of the center by means of nervous stimuli, such as stimulation of the exposed pleuras or peritoneum; and cutting of the efferent paths from the center to the lungs. On the whole it is certain that in pulmonary edema with ligation of the aorta the nervous factor assumes such an importance that the reflexes are blocked and edema does not appear.

Adrenalin Method

Pulmonary edema caused by adrenalin[27] was studied by Huchard, Claude, Josere and Cavina and more recently by Glass, Luisada, Boggian, Antoniazzi and others in the medical clinic of Padova, Italy.[27] Loeb,[77] in 1926, Auer and Gates,[78] in 1917, and Meltzer,[79] in 1904, also produced pulmonary edema with adrenalin.

Acute pulmonary edema caused by adrenalin in animals offers notable similarities with edema in human beings. It occurs suddenly, displays a picture of dyspnea, hypertension and tachycardia, and soon causes the same rose-colored froth at the mouth and nose of the animals and similar alterations of the lungs.

A systematic study was done by Luisada[27] with 250 rabbits to determine the dosage necessary to cause the death of the animals with acute pulmonary edema. He was able to stabilize the dose so as to produce pulmonary edema in 90 per cent of the animals. With these doses of adrenalin the following facts were noted: some narcotics and sedatives prevented pulmonary edema in a significant percentage of the treated cases, and the effective dose of the narcotic did not need to be strong enough to bring about a state of narcosis. Luisada proved that with the use of a complex mixture containing morphine, papaverine and chloretone 20 out of 21 animals could be saved, even when the dose of adrenalin was raised 50 per cent. He demonstrated that this action was not due to decreasing the hypertension of adrenalin, since pituitrin causes a hypertension similar to that of adrenalin but does not cause edema. Lowering the blood pressure due

to adrenalin by means of drugs that inhibit sympathetic stimulation — such as ergotoxine — did not lower the percentage of animals dying with edema.

The probable action of these drugs is depression of the central-nervous-system centers. The drugs with a beneficial arresting action on the edema of adrenalin are papaverine, chloretone, chloral, morphine and luminal — a group of varied compounds with varied actions. This conclusion is not a comforting one, since it is far from being simple, but it is perfectly justified considering the multiplicity of reflexes that are simultaneously being transmitted and the numerous centers that are affected.

Antoniazzi found that the injection of a fatal dose of adrenalin into a rabbit treated and prepared with an open thorax or abdomen rarely provoked pulmonary edema.

In a further investigation of pulmonary edema caused by adrenalin, Luisada[27] tested the action of the drug on the nervous centers and the effect of cephalic hypertension separately, using cross-circulation experiments. In the first experiment the circulation of the head of one animal was connected with the body of a donor animal, only nervous connections being left between the head and the lungs of the recipient animal. Injection of adrenalin into the donor animal then perfused the head of the recipient with adrenalin, and after a short time typical pulmonary edema occurred. In the second experiment, which was performed with one animal, the circulation of the head was isolated and connected with a perfusing apparatus, being connected to the lungs by nervous routes only. The head was then perfused with Tyrode's solution under elevated pressures, and pulmonary edema soon followed. But the most interesting result was the fact that with a similar technic Luisada was able to provoke pulmonary edema in dogs and cats alike — animals that habitually do not show pulmonary edema from adrenalin. In the dog, Luisada elevated the pressure in the cerebral vessels to 200 mm. of mercury and in the cat from 200 to 250 mm. In both animals an intense serosanguineous pulmonary edema resulted. The simultaneous registration of the aortic pressure, performed on the cat, showed that the beginning of the cerebral hypertension is accompanied by bradycardia and aortic hypotension, both of a reflex nature. Pulmonary edema appearing in this way is thus a reflex phenomenon.

Luisada and Sarnoff[80] recently extended these observations. They found that large intravenous infusions of saline solution in dogs rarely produced pulmonary edema but the same infusions introduced into both common carotids under a pressure of 280 to 300 mm. of mercury caused pulmonary edema in most cases. This edema was minimized or prevented by intratracheal positive pressure, artificial respiration, carotid-sinus denervation, bleeding during the infusion, ergotamine, curare, narcotics (barbital, phenobarbital, morphine and chloral), procaine subcutaneously, atropine and physostigmine.

To determine whether the carotid-aortic stimuli alone provoked pulmonary edema, Luisada injected an effective dose of adrenalin into animals with all cerebral circulation ligated except one vertebral artery, effective cerebral hypertension being thus prevented. Half the animals so treated died; it appears that the carotid reflexes are contributory but are not so effective alone as when combined with those from the cerebral vessels.

The significant factor in adrenalin-produced pulmonary edema is the effect of hypertension; it is not a general or a pulmonary hypertension that matters, but in a small degree the hypertension in the aorta and in a large degree the hypertension in the carotid and cephalic vessels. This hypertension activates a reflex arc that determines the sudden increase in the permeability of the pulmonary vessels and the consequent pulmonary edema.

Toxic Methods

The irritating gases have long been known to cause pulmonary edema, and this was held to be due to direct toxic action on the lung capillaries. The following passage from a discussion held in England on these gases before World War II is interesting:

> It was shown (Aschoff, Flury, Gildemeister, Heitzmann, Koch, Lagueur, Magnus, Mayer, Ricker, etc.) that amongst many other interesting observations on the functional impairment following phosgene poisoning, section of both vagus nerves in animals largely prevented the onset of the classical signs and symptoms. From a large and varied series of experiments, these investigators concluded that the action of phosgene could be divided into two categories: (1) The irritant effect of the hydrochloric acid which is liberated as phosgene passes into solution. This irritation involved the whole respiratory tract and, in concentrations used in gas warfare, could be of little importance. (2) The more direct effect of phosgene on the nerve endings of the pulmonary vagus. It appeared that it is this action on the vagal nerve endings which, after a latent period, led to the development of pulmonary edema. So far as could be found in the literature, these experiments have never been refuted.[81]

Teisser[29] listed as toxic pulmonary edemas those produced experimentally following ingestion of potassium iodide, iodoform and pilocarpine, or following intravenous injections of muscarine, chlorine water, prussic acid, amyl nitrite and methyl salicylate. Teisser believed that toxins played an important part in the pathogenesis of the disease in human beings.

The MacKenzies[59] found that thiourea and phenyl-thiourea produced pulmonary edema, and Drinker[12] reported a thiourea derivative that caused pulmonary edema when given by any route.

In the light of German studies on the effect of the vagus on the pulmonary edema of phosgene, experimental edemas with toxins must be thoroughly re-evaluated, and it is possible that a similar nervous factor will be found in each case.

Nervous Mechanisms

Jores[82] was able to produce pulmonary edema by irritation of the small bronchioles with a blast of air or carbon dioxide. He found that faradization of the parenchyma of the lung led to small areas of hemorrhagic edema, and that gentle faradization of the peripheral stump of the vagi for ten minutes also led to pulmonary edema. Dubel[42] states that Mercier caused acute pulmonary edema by stimulation of the peripheral vagus. He credits Vincent and Bernard with the production of edema by stimulation of the nerves of the second, third and fourth thoracic segments in animals. Broutin[46] cites Brincourt's experiment eliciting acute pulmonary edema by stimulation of the posterior roots of the lower cervical and upper thoracic cord, von Frey's demonstration of pulmonary edema following bilateral vagotomy in rabbits, and Kraus's discovery that injections of physiologic saline produced pulmonary edema only if preceded by bilateral vagotomy and that intense vasodilatation in the pulmonary vessels preceded the onset of the edema. Brunn[83] and Farber[7, 72] recently repeated and extended the work of von Frey and Kraus, whereas Short[84] obtained conflicting results.

Luisada[27] writes that in a series of animals subjected to extirpation of the cerebral cortex, optic thalami and corpus striatum and injected with adrenalin after twenty-four hours most of the animals died, proving that these extirpations had no protective value. In a second series of animals the cord was severed between the second and third cervical vertebras, the vagi were cut and the carotid arteries ligated, so that the animals were almost completely deprived of central connections since the sympathetic fibers do not carry impulses cephalad. These animals were injected with adrenalin, and pulmonary edema did not appear.

Glass[85] made lesions in the corpora quadrigemina, with destruction of the anterior quadrigeminal body on one side, causing a large lesion in the neighborhood of the third ventricle. Out of 15 animals so treated, only 7 developed pulmonary edema; unilateral damage in the region of the third ventricle was thus demonstrated to be capable of protecting a large percentage of animals from the edema that inevitably results from the injection of adrenalin. Glass extended the work on the sympathetic chain and found that unilateral extirpation of the chain below the superior cervical ganglion saved 70 per cent of the animals and was more effective than bilateral extirpation.

Luisada and Boggian[2, 27] claimed that extirpation of the stellate ganglion is the simplest and best technic for denervation of the lung since this procedure has the advantages of interrupting four fifths of the efferent fibers to the lungs and of cutting a large part of the afferent fibers from the heart, the aorta and the lungs. Extirpation of the stellate ganglion leaves the afferent fibers of the vagus, the depressor nerves, the phrenic nerves and the carotid sinus; some efferent fibers that go directly from the superior cervical ganglion or the second or third thoracic ganglion to the lungs occasionally remain. Removal of the stellate ganglion, however, is certainly the operative measure in which the lung can be deprived of the maximum part of its nerves with the minimum trauma. Wishing to exclude the consequences of operation, Luisada compared his results immediately after and twenty-one days after operation to the technic of Glass.[85] Using a 2-mg. dose of adrenalin he found that 33 per cent of the animals died with pulmonary edema twenty-four hours after unilateral cutting of the sympathetic chain below the superior cervical ganglion, whereas if twenty-one days elapsed before adrenalin injection 83 per cent died. Unilateral excision of the stellate ganglion followed in twenty-four hours by adrenalin killed 33 per cent of the animals, and after twenty-one days only 14 per cent died. Bilateral cervical sympathectomy below the superior cervical ganglion followed in twenty-four hours by a 2-mg. dose of adrenalin permitted 100 per cent fatalities, but with bilateral excision of the stellate ganglion before the administration of adrenalin only 20 per cent died. Further experiments showed that cutting the phrenic nerve, although it did not greatly improve the absolute mortality, diminished slightly the number of cases of pulmonary edema. The grave consequences of the operation — in fact, the death of the animals by suffocation during the attack of dyspnea — make the effects of phrenicotomy worse than the higher percentage of pulmonary edema resulting from sympathectomy alone.

The fundamental facts that point to a direct or indirect involvement of nervous factors are as follows: electric stimulation of the nerve trunks or the pulmonary parenchyma provokes pulmonary edema; cutting the vagi facilitates the appearance of acute pulmonary edema by eliminating the control and inhibition of the central pulmonary vessels innervated only by the sympathetic system; acute pulmonary edema can be provoked by a strong dose of adrenalin injected intravenously — pulmonary edema from adrenalin is not directly determined by the arterial hypertension in the systemic or pulmonary circulation; the substances that depress the respiratory center inhibit pulmonary edema from adrenalin; such edema can be averted with the preventive use of narcotics that have varied loci of action; cutting the cervical cord impedes pulmonary edema from adrenalin, but several nervous-system lesions above the hypothetical center do not inhibit the edema; puncture of the anterior corpus quadrigeminus on one side inhibits this type of pulmonary edema in a certain number of cases; cutting the sympathetic chain prevents edema in some cases, but a better operation consists in bilateral removal of the stellate ganglion,

which impedes the edema in three quarters of the cases; with the use of isolated perfusion of the head or cross-circulation it is possible to cause pulmonary edema by means of hypertension in the cephalic vessels alone; no maneuver that tends to increase the pressure in the pulmonary circulation causes edema if the thorax is open, but the occurrence of pulmonary edema is constant after ligation of the aorta with the thorax closed; depression of the nervous center with narcotics or reflexly with pleural or peritoneal stimuli prevents edema with the ligaturing of the aorta, as does cutting of the sympathetic pathways; and edema from ligation of the aorta is thus explained by a basic reflex and the fact that the depression of the center impedes it, interrupting the same reflex arc.

The overall picture derived from the experimental data of Luisada can be described by the following three points. Merely mechanical and humoral factors on the heart and lungs cannot cause experimental pulmonary edema, which always occurs via a nervous mechanism, as in that produced by adrenalin and by ligation of the aorta. It is possible to cause pulmonary edema by modifying only the circulation of the head, and this is determined by a hypertension in the cephalic vessels. It is possible to cause pulmonary edema by electric stimulation of the nervous pathways.

Other Methods

Moon[8] reported the production of pulmonary edema by various shocking procedures, such as intravenous muscarine, iodine, serum in sensitized animals, perfusion of heart-lung preparations with old defibrinated blood, following burns, after intravenous bile salts or bile and following prolonged intestinal obstruction. He remarks that pulmonary edema was a conspicuous gross feature when death was somewhat delayed. It is difficult to determine whether the pulmonary edema observed in these cases was merely part of a generalized picture of shock, with its effects on the capillaries, or whether it was something more specific.

Theories of Pathogenesis

Masius,[86] at the International Congress of Medicine in Paris in 1900, reviewed the theories of pathogenesis of acute pulmonary edema, including the mechanical theory advanced by Lower, Brown-Séquard, Ranvier, Bouillaud, Cruveilhier, Cohnheim, Welch, Sahli, Grossman, Chatin, Guinard, Winckler and Basch and the secretion or bronchorrhea theory supported by Hamburger and Heidenhain. Changes in permeability or osmotic pressure of the blood were blamed by Starling, Winter, Theaulon and Dreser. A vasomotor action was suggested by Bouveret[87] in 1890, whereas Huchard,[88] in 1892, proposed a reflex condition initiated by irritation of the plexuses surrounding the heart and lung. Dieulafoy,[89] in 1896, believed that nephritis and a toxic effect on the lung capillaries accounted for all cases. Reimann[30] suggested multiple causes, as did Teisser[29] and Huchard.[88] Harrison[23] reviewed the problem of cardiac asthma.

Although it seems plausible that there are toxins that specifically alter the permeability of the pulmonary vessels, the evidence that vagotomy prevents the pulmonary edema of phosgene poisoning inevitably raises some question regarding the actual mechanism of such toxins. This subject must be investigated further.

Luisada[34] recently presented the neurogenic theory in a complete form, as follows:

> According to this concept the attack is the result of acute congestion of the pulmonary vessels followed by transudation in the alveoli. The immediate cause of this condition is an intense stimulation of the vasodilator nerves of the lungs due either to a lesion of the nerve centers or to reflexes arising in the various viscera. The pulmonary edema in persons with skull injuries, with subarachnoidal hemorrhage, and with poliomyelitis is included in the first class, as the lesion is central. The pulmonary edema of drowning people, and, to a partial extent, that of soldiers subjected to war gases, should be included in the second class, as reflexes arising in the mucosa of the larynx, of the trachea, and of the bronchi seem to be the main causes of the attack. A multiple reflex probably occurs in hypertensive patients where the nerve receptors of the aortic arch, the carotid sinus, and of the heart wall are excited by distention. A simpler reflex causing typical attacks may occur in the stimulation either of the heart receptors (acute ischemia as in coronary occlusion) or receptors of the esophagus and of abdominal organs.

Therapy

In an extensive review of the problem presented by the therapy of pulmonary edema Luisada[34] points out that the followers of the heart-failure theory advocate drugs stimulating the myocardium, the vasomotor center, the peripheral arteries, the carotid sinus and the respiratory center — such as digitalis, ouabain, strophanthin, camphor, Coramine, caffeine, metrazol and ether and that most clinicians also recommend sedatives and narcotics that depress the central nervous system, the autonomic nervous system and smooth-muscle fibers of the vessels — for example, morphine, phenobarbital, chloretone, chloral, atropine and papaverine — and thereby imply a belief in a neurogenic theory. Both theories include recommendations of certain mechanical procedures designed to lessen pulmonary congestion or to improve oxygenation of the blood. He suggests that the sedative drugs are in some ways antagonistic to stimulants, so that if the sedatives are used the stimulants should obviously not be employed. The action of the stimulating drugs is regarded as so complex that their use is objectionable even when the theory of left ventricular failure is accepted.

Luisada found the following drugs valuable: morphine, especially in patients with pain; atropine, especially when the central nervous system is involved; phenobarbital in cases with central-nervous-system lesions and no abnormality of blood pres-

sure; chloral and chloretone in patients with high blood pressure; and papaverine in patients with coronary occlusion. He concludes that chloretone, chloral, sodium phenobarbital, papaverine hydrochloride, atropine sulfate and morphine sulfate may safely be injected intravenously and that during the acute attack digitalization and stimulants should be avoided.

Luisada's therapy for the prevention of attacks includes: digitalis for subacute insufficiency of the heart; morphine subcutaneously, in addition to atropine and phenobarbital, following skull trauma, since patients usually develop pulmonary edema six to twenty-four hours after injury; and opium and belladonna by mouth in cases of recurrent pulmonary edema. He also considers oxygen of value in the acute attacks.

Carlisle,[33] in 1943, presented a series of 316 cases seen in the previous nine years of workers exposed to noxious gases. He treated all patients with 100 per cent oxygen under atmospheric pressure, with a positive pressure of 1 to 6 cm. water during expiration. He observed no fatalities. The rest of this therapy consisted solely of strict bed rest. This is indeed a remarkable record.

Barach et al.[90] treated 8 patients with acute pulmonary edema successfully with oxygen under a pressure of 5 to 7 cm. of water for from ten to sixty minutes. Their conclusions regarding the effect of therapy were as follows: a decreased volume of blood entering the right heart leads to decreased pulmonary capillary pressure and, in turn, to decreased transudation of serum and cells; some blood may be squeezed into the left auricle; the increased alveolar pressure drives serum and cells back into the capillaries; a questionable effect on the resultant anoxia of pulmonary edema was observed.

Donzelot and Ménétrel[57] reported a case of recurrent pulmonary edema in a thirty-five-year-old woman with a surgical menopause and increasing asthma. Bleeding, morphine and ouabain were used to relieve individual attacks, but recurrence continued. Finally the authors infiltrated 20 cc. of a 1 per cent solution of novocain in the region of the left stellate ganglion under fluoroscopic direction, with complete relief of the pulmonary edema and asthma. The heart and lungs soon returned to and remained normal. They quoted a similar case reported by Gounelle.

Summary

The syndrome of acute pulmonary edema is reviewed. The x-ray appearance, pathology and pathologic physiology are briefly described, and diseases in which this syndrome appears are listed. Experimental studies that emphasize the importance of the nervous system in the precipitation of pulmonary edema are reviewed. Therapy is discussed in the light of recent experimental studies.

The inadequacies of previously accepted explanations of the pathogenesis of acute pulmonary edema are becoming increasingly evident, and a new field of investigation, which promises to be fruitful in providing a more satisfactory explanation of this syndrome and a more rational therapeutic approach, lies ahead.

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NEW HAMPSHIRE MEDICAL SOCIETY

Proceedings of the One Hundred and Fifty-Fifth Anniversary

THE scientific session of the New Hampshire Medical Society convened at 9:30 o'clock on the morning of May 14, 1946, with President Richard W. Robinson, of Laconia, presiding.

The first item on the program was a motion-picture film entitled "Angina Pectoris," presented through the courtesy of Brewer and Company, Incorporated. The President introduced Dr. Paul C. Barton, medical director of Brewer and Company, who before the war was director of the Bureau of Investigation of the American Medical Association and during the war served as executive officer of the Procurement and Assignment Service. Dr. Barton presented the motion picture. A paper "Autopsy Service — Mary Hitchcock Hospital" was then presented by Dr. Ralph E. Miller, of Hanover. This was followed by a paper by Dr. Edwin B. Astwood, of Boston, Massachusetts, entitled "Present Status of the Medical Treatment of Thyrotoxicosis." Dr. Louis H. Bauer, a trustee of the American Medical Association, then presented a paper "The Medical-Care Problem in the United States." The morning session was concluded at 1:00 p.m.

The afternoon session opened with the awarding of fifty-year certificates to Dr. H. Sheridan Baketel, of Greenland, and Dr. Oscar C. Young, of Charlestown. Dr. Baketel, on receipt of his certificate, spoke as follows:

> The presentation of this certificate, commemorating my continuous membership in the New Hampshire Medical Society for fifty years, is fraught with especial significance.
>
> To some men, it might merely mean that they had been in the Society for half a century, exactly as if they had voted the same national ticket for a similar period or carried the same watch. To me, this occasion reaches deeply into my inner consciousness. When I was a small boy in Greenland, riding with my medical idol and inspiration, the late Dr. William Oliver Junkins, of Portsmouth, I learned that in taking on the great responsibilities of medical practice, the physician is duty bound to make himself a living part of his profession. This fact was accentuated in my mind while in Dartmouth. The two men who then had such a major part in shaping the minds and ideals of medical students, Drs. Carlton P. Frost and William T. Smith, impressed us with the necessity of allying ourselves with the Society at the earliest opportunity — advice that I followed.
>
> Next to the award of my medical degree in 1895, my proudest moment was the day I received from the secretary of the New Hampshire Medical Society, and one of my most respected Dartmouth professors, the late Dr. Granville P. Conn, the certificate of membership, dated June 7, 1896. That parchment is one of my most treasured possessions today.
>
> I belong to fifteen or more medical associations and am proud to be a life fellow of the American College of Physicians, but the pleasure of election to these professional groups was never accompanied by the thrill that coursed through my body on that memorable June 7.
>
> Destiny decreed that the past forty-four years should be spent in New York City or adjoining New Jersey, and although I was active there as a practitioner, medical-school professor, editor and research worker, my spiritual self was ever in the Granite State.
>
> My beloved father, the late Rev. Dr. Oliver S. Baketel, brought his family from our native Ohio to Newfields in 1877, and there at the age of four my interest in the State was aroused. It was enhanced at Portsmouth High School, Phillips Exeter Academy and Dartmouth College, where we were taught to venerate the Granite State.
>
> New Hampshire became almost an obsession. I have always read *The Union*, which has daily followed my peregrinations into exotic climes as well as being delivered at home. To me, except by the accident of birth, I am a New Hampshireite to the very core.
>
> One can easily imagine my delight, when in 1940 it became possible to acquire a venerable house on the Parade in Greenland, nearly opposite the old parsonage in which I had passed such a happy young boyhood, and in being near Portsmouth, where many of my formative years were delightfully passed.
>
> In looking about this group, I miss the faces of some of the medical giants of the days when I joined the Society: Barry and Parsons, of Portsmouth, Stillings and Walker, of Concord, McQuesten and Greely, of Nashua, Flanders, Boutwell, French, Towne and Robinson, of Manchester, Jarvis, of Claremont, Prouty, of Keene, Staples, of Franklin, Smith, of Hudson, McGregor, of Littleton, Boynton, of Lisbon, Mitchell, of Epping, and Nute, of Exeter, to mention only a few. It is a real satisfaction to have known those men who have now passed away, and many other of the splendid physicians who then upheld the dignity of the New Hampshire profession as true followers of Aesculapius.
>
> For these reasons, I am proud to accept the certificate of fifty-year membership.
>
> As I wrote not long ago in *The Troubadour*: "It is my hope that from my Greenland home, I can continue to look out over life calmly and steadfastly, until the world for me loses itself in the twilight of time and eternity."

The President then requested the delegates from other New England states to stand up and make themselves known.

The report of the House of Delegates was given by the secretary-treasurer, Dr. Carleton R. Metcalf.

Dr. Robinson then presented the president-elect, Dr. Ralph W. Tuttle who acknowledged the applause of the audience.

President Robinson spoke as follows:

> I wish to emphasize something that Dr. Metcalf mentioned in the report of the House of Delegates, because I think it is one of the most important projects that the Society as a whole has to consider at the present time. Since we have a small society that is quite well integrated, we have an unusual opportunity to do exceedingly worthwhile and helpful work for the whole of the medical-care problem in this country, if we can undertake, on a voluntary insurance basis, the care of the indigent. The problem has been given some consideration, and it seems feasible to work out a scheme that will be satisfactory both to the welfare agencies and to the medical profession in the State, with the thought that we shall no longer have to be subject to the fees that we have charged for the rendering of such service, on a basis that belittles, in some ways, the medical profession. Of course, during the depression, it was perfectly proper, but because we established a

precedent, evidence that the present fee is being thought of as a proper fee for minimum medical care has grown up in the minds of the people that administer the program.

I should like to see that situation altered and to have the indigent cared for on the same basis as the minimal service charge that we make in the indemnity policy of the Blue Shield. Unfortunately, whereas the co-operation as a whole throughout New Hampshire has been good, there are certain physicians who have not believed that their own opinions regarding this means to take care of the costs of medical care are justifiable. If we could even get the co-operation of such men to the extent that they would be willing to try this as an experiment, so that we could get co-operation throughout the State, it would be possible for us to go ahead with this program. So long as there is any part of the State that is not co-operating, of course, it is apparent that the welfare agencies cannot take up their end of this particular scheme.

Another point that should be emphasized is that the Blue Shield plan that we are operating in New Hampshire is your plan; it does not belong to one physician but to every physician. The Blue Shield, which is simply the physical agent of the physicians in the State, can be altered as policies can be altered, on the basis of any justifiable and reasonable recommendations. You men should consider yourselves welcome to all the meetings of the professional sessions of that organization, and I believe that the directors of the organization want and hope for all possible criticism, because the only desire they have is to make the thing work, both to the benefit and satisfaction of the profession and to the satisfaction of the people that we try to take care of on that basis.

Dr. Lendon Snedeker, of Boston, chairman of the Massachusetts Committee of the American Academy of Pediatricians, then spoke as follows:

I am speaking for Dr. Colin Stewart, and I am sorry that he could not be here today. I am the executive secretary for the study of the American Academy of Pediatricians in Massachusetts. The study of child health services that the Academy has started is an attempt to obtain a physician's estimate of child health in the United States — facilities for serving children and their extent and location, such as those found in hospitals and in clinics and other health services outside institutions, including the schools. The study is also attempting to find out the contribution to health service to children made by doctors and dentists in every state, and is looking into the question of pediatric education, a topic that is being handled on a national level.

The completion of a project of this sort will take some time, probably another year and a half. Headquarters have been set up in Washington, and Dr. John Hubbard, formerly of Boston, is the director for the study. A national committee, headed by Dr. Warren Sisson, of Boston, is responsible for the over-all conduct of the study, for which a budget of nearly half a million dollars has been raised. Already, over thirty states have been organized and have started on the job; successful completion of the project appears possible.

Dentists are being reached through the state dental societies in general. Hospitals are being reached by the pediatricians and physicians around the country and the district health officers. The nurses and the doctors responsible for local health services are looking into clinics and extrainstitutional facilities.

The Academy has gone on record as being against the present health legislation before Congress, on which it believes this study, and the knowledge that it is being carried out, will have some deterrent effect. It also expects that the information disclosed by this study will be used on both national and state levels for laying a sound basis for any future health legislation that may come about. Much of the planning is up to physicians, and the way to achieve sound planning is for the doctors to get the facts. We are therefore asking you, when the questionnaire comes around, to give us facts on which we can say that this is what the doctors of the country are doing all the time for the children and the children's health services.

Dr. Forrest J. Drury, director of the New Hampshire Veterans Service, spoke as follows:

I was glad this morning to hear Dr. Bauer state that it was the policy of the present medical officials of the Department of Medicine and Surgery of the Veterans' Administration to keep the physician-patient relation and to provide care for veterans for their service-incurred disabilities, in their own communities and by their own physicians. That is exactly what we wish to do.

We shall authorize any physician registered in New Hampshire to care for any veteran in his community if that physician will co-operate with us in the very necessary paper work. I know that they will immediately say, "red tape," when they see a government form, but we have reduced that, we believe, to the irreducible minimum of forms, and I doubt that we will have any more forms to fill out than the Blue Shield has. We believe that our fee table is comparable to that of the Blue Shield.

If any veteran reports to any physician in the state with a letter that is sent to every veteran when his case has been adjudicated and grants service treatment for a service-connected disability, you are perfectly safe in going ahead and rendering the treatment, if you will report that fact to my office within five days after treatment is rendered. I must have that information. We work on a budget, and I must record the case on the budget within five days.

Veterans are entitled to hospital treatment in civilian hospitals in emergencies, but only for service-connected disabilities; the time consumed in getting the patient to a veterans' hospital and the distance must be considered to be dangerous. Such facts must be reported to my office within twenty-four hours. With outpatient reporting, five days are allowed. But when veterans are placed in hospitals without prior authority first, the case must be reported to my office within twenty-four hours. It is always best to get the authority beforehand.

We have sent letters to every physician on our list, with the probable exception of some men returning from the service, regarding payment of fees for examinations to determine the need for hospitalization. Until last October, examinations for nonservice-connected disability could not be paid for. That meant that the doctors throughout the State were doing a great deal of work, and either the veteran paid for the examination or the doctor did not get paid for it. Under the new setup, however, and under a ruling last October, if a doctor is making an examination to determine the need for hospitalization, we can pay a fee of $3.00, and if the call is made between 7:00 p.m. and 7:00 a.m. the fee can be $5.00.

We recently sent letters to all physicians, telling them of our twenty-four-hour service. There is a man on call all night in the office and on Sundays and holidays. Therefore, the number of the Veterans' Administration can be called any time of the day or night, seven days in the week.

Another point Dr. Bauer mentioned was the fact that these services exist in some states. There are two different setups. One is known as the New Jersey and the other as the Michigan setup. I hope that this society, sometime in the near future, may see fit to set up a similar service. I prefer the Michigan to the New Jersey plan. The latter is not greatly different from the plan in New Hampshire, except that the society furnishes the names of physicians who have agreed to work on this plan. The Veterans' Administration sends out the forms. Under the Michigan plan, a contract with the Veterans' Administration takes care of everything. A physician in the veteran's community is designated to take care of the particular condition; the society then bills the Veterans' Administration. That, to my way of thinking, is the ideal plan. Under the Michigan plan, we get the names from the state society, instead of individually or from hospital staffs.

I should like to say that if there is any group of physicians, hospital staff, city or county society that would care to have me come at any time to any meeting, to tell them the whole story, I shall be very glad to do so.

Dr. John C. Leonard, a director of the Joseph H. Pratt Diagnostic Clinic in Boston, Massachusetts, then presented a paper entitled "Hypertension."

This was followed by a paper by Dr. Clay R. Murray, of New York, the subject being "Handling of Common Injuries to the Knee Joint."

Dr. John T. King, of Baltimore, professor of medicine at Johns Hopkins University School of Medicine then presented a paper entitled "Acute Chest Episodes Caused by Pulmonary Embolism: Differential diagnosis and treatment."

A financial report from the Trustees for the period beginning January 1, 1945, and ending December 31, 1945, was then presented, as follows:

GENERAL FUND

Receipts:		
Balance on hand January 1, 1945		$4,775.11
Nashua Trust Company interest		6.70
Portsmouth Trust and Guarantee Company interest		24.56
New Hampshire Savings Bank interest		26.37
U. S. Series G bonds interest		125.00
Total		$4,957.74
Expenditures:		
U. S. Series G Bonds	$2,000.00	
Cash balance December 31, 1945		$2,957.74
U. S. Series G bonds		5,000.00
Total Fund		$7,957.74

BARTLETT FUND

Receipts:		
Balance on hand January 1, 1945		$2,998.92
Portsmouth Savings Bank interest		71.04
U. S. Series G bonds interest		50.00
Total		$3,119.96
Expenditures:		
Trustees of Dartmouth College Repairs on animal pen at Medical School	$1,000.00	
Cash Balance December 31, 1945		$2,119.96
U. S. Series G bonds		2,000.00
Total fund		$4,119.96

PRAY FUND

Receipts:		
Balance on hand January 1, 1945	$291.08	
Strafford Savings Bank interest	4.37	
U. S. Series G bonds interest	25.00	
Total receipts and cash balance December 31, 1945		320.45
U. S. Series G bonds		1,000.00
Total fund		$1,320.45

BURNHAM FUND

Receipts:		
Balance on hand January 1, 1945	$1,064.01	
N. H. Savings Bank interest	21.28	
U. S. Series G bonds interest	25.00	
Total receipts and cash balance December 31, 1945		$1,110.29
U. S. Series G. bonds		1,000.00
Total fund		$2,110.29

BENEVOLENCE FUND

Receipts:		
Balance on hand January 1, 1945	$3,239.81	
Dr. Metcalf	100.00	
N. H. Savings Bank interest	65.51	
U. S. Series G bonds interest	75.00	
Total receipts and cash balance December 31, 1945		$3,480.32
U. S. Series G bonds		$3,000.00
Total fund		$6,480.32

HOWARD N. KINGSFORD, M.D.
GEORGE C. WILKINS, M.D.
SAMUEL T. LADD, M.D.

sure; chloral and chloretone in patients with high blood pressure; and papaverine in patients with coronary occlusion. He concludes that chloretone, chloral, sodium phenobarbital, papaverine hydrochloride, atropine sulfate and morphine sulfate may safely be injected intravenously and that during the acute attack digitalization and stimulants should be avoided.

Luisada's therapy for the prevention of attacks includes: digitalis for subacute insufficiency of the heart; morphine subcutaneously, in addition to atropine and phenobarbital, following skull trauma, since patients usually develop pulmonary edema six to twenty-four hours after injury; and opium and belladonna by mouth in cases of recurrent pulmonary edema. He also considers oxygen of value in the acute attacks.

Carlisle,[83] in 1943, presented a series of 316 cases seen in the previous nine years of workers exposed to noxious gases. He treated all patients with 100 per cent oxygen under atmospheric pressure, with a positive pressure of 1 to 6 cm. water during expiration. He observed no fatalities. The rest of this therapy consisted solely of strict bed rest. This is indeed a remarkable record.

Barach et al.[90] treated 8 patients with acute pulmonary edema successfully with oxygen under a pressure of 5 to 7 cm. of water for from ten to sixty minutes. Their conclusions regarding the effect of therapy were as follows: a decreased volume of blood entering the right heart leads to decreased pulmonary capillary pressure and, in turn, to decreased transudation of serum and cells; some blood may be squeezed into the left auricle; the increased alveolar pressure drives serum and cells back into the capillaries; a questionable effect on the resultant anoxia of pulmonary edema was observed.

Donzelot and Ménétrel[87] reported a case of recurrent pulmonary edema in a thirty-five-year-old woman with a surgical menopause and increasing asthma. Bleeding, morphine and ouabain were used to relieve individual attacks, but recurrence continued. Finally the authors infiltrated 20 cc. of a 1 per cent solution of novocain in the region of the left stellate ganglion under fluoroscopic direction, with complete relief of the pulmonary edema and asthma. The heart and lungs soon returned to and remained normal. They quoted a similar case reported by Gounelle.

Summary

The syndrome of acute pulmonary edema is reviewed. The x-ray appearance, pathology and pathologic physiology are briefly described, and diseases in which this syndrome appears are listed. Experimental studies that emphasize the importance of the nervous system in the precipitation of pulmonary edema are reviewed. Therapy is discussed in the light of recent experimental studies.

The inadequacies of previously accepted explanations of the pathogenesis of acute pulmonary edema are becoming increasingly evident, and a new field of investigation, which promises to be fruitful in providing a more satisfactory explanation of this syndrome and a more rational therapeutic approach, lies ahead.

24 North Broadway

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88. Huchard. Cited by Masius.[86]
89. Dieulafoy. Cited by Masius.[86]
90. Barach, A. L., and Martin, J., and Eckman, M. Positive pressure respiration and its application to treatment of acute pulmonary edema. *Ann. Int. Med.* **12**:754-795, 1938.

or mesenteric thrombosis. It seems to me that we can rule out a number of those conditions by the subsequent course of events. I do not see how a lesion of the biliary system or acute pancreatitis could behave in this way. I do not believe that the subsequent intestinal symptoms would have developed on that basis.

How about a dissecting aneurysm? Again, I do not believe that the gastrointestinal symptoms could be accounted for in that way. At the end of seven days a large stool containing old blood was passed. Also, later on, a mass appeared that was not felt at admission — pelvic examination was done at that time and did not show it; it developed later. Could this have been something in the lower abdomen such as a twisted ovarian cyst or a volvulus of the sigmoid? I do not believe that either could account for the onset of such severe upper abdominal pain that disappeared completely in two days. It seems to me that we must find some lesion that will cause pain referable to the upper abdomen impairing the blood supply to the bowel in a manner that will allow some bleeding into the intestinal tract, so that that blood will later be passed as old blood, and a lesion that at the same time will give a picture of partial intestinal obstruction. I think that we can exclude the colon on the basis of the symptomatology, and I believe that we must place this lesion fairly low down in the small bowel. I believe that the likeliest thing that occurred in this woman was a mesenteric thrombosis. There are obviously a number of things that do not fit that picture, such as the lack of abdominal signs and the fact that the white-cell count was only 10,000. In spite of that, however, it seems to me that mesenteric thrombosis fits the picture better than anything else I know of, and I shall make that diagnosis.

Dr. Tracy B. Mallory: Is there anyone who would like to make a suggestion?

Dr. Maurice Fremont-Smith: Could the patient have had an intussusception that cleared up?

Dr. Bartlett: I think that she could have — one that was spontaneously relieved?

Dr. Fremont-Smith: Yes; but in adults intussusception is usually associated with polyps or carcinoma.

Dr. Bartlett: It is usually associated with some tumor.

Dr. Mallory: One would probably expect previous attacks of incomplete obstruction in such a case.

A Physician: How about internal hernia?

Dr. Bartlett: Do you mean by that a loop caught under a band?

A Physician: Yes.

Dr. Bartlett: I think that she could have had that, but the symptoms were mild and the obstruction was incomplete. I also think that that would be less likely to give bleeding in the bowel.

Dr. Mallory: Dr. Welch, will you tell us your opinion before operation?

Dr. Claude E. Welch: Perhaps I should first apologize for the surgical treatment. One might wonder why operation was delayed for four days after the patient came to the hospital. When she came in I could not even be sure that she had intestinal obstruction. She had a history of severe pain occurring three hours after drinking some cocktails, described by the physician, who had sampled them himself, as "sulfuric acid." She was so well at the end of almost a week's sickness that when she came to the hospital I thought that perhaps she had gastritis. We elected to treat her conservatively. At the end of twenty-four hours, it was obvious that there was obstruction. There really was fecal material coming out of the Miller–Abbott tube. We decided to give a barium enema and to study the situation further before exploration. As time went along the preoperative diagnosis favored by Dr. Arthur W. Allen was an intussusception because of the presence of the abdominal mass and the bleeding by rectum, together with intestinal obstruction. There were several votes in favor of the diagnosis of Meckel's diverticulum. In other words we all thought of the rare lesions and we also thought that, whatever the cause of the obstruction, it was a nonstrangulating type.

Dr. Mallory: Will you describe the operative findings?

Dr. Welch: When the abdomen was opened bloody fluid was immediately apparent. This mass that had been variously interpreted as fibroid uterus or some lesion associated with the bowel was a mass of gangrenous bowel that had been caught behind a simple band. As soon as the band was cut, the whole intestinal tract righted itself, but it was necessary to resect this entire loop of bowel. The patient had had no previous abdominal operation and no previous infections anywhere in the pelvis. We could not make out the cause of the bands but there were two present, one of which had caused the trouble.

Clinical Diagnosis

Small-bowel obstruction.

Dr. Bartlett's Diagnosis

Mesenteric thrombosis.

Anatomical Diagnosis

Strangulation of bowel by adhesive band.

Pathological Discussion

Dr. Mallory: The operative specimen we received showed nothing but gangrenous bowel. No cause was ever determined for the adhesive band.

Dr. Alfred Kranes: What was the primary lesion?

DR. MALLORY: An adhesive band in a woman with no previous operation and no infection. There was secondary thrombosis of the mesenteric vessels.

DR. FREMONT-SMITH: If we knew that she had a band, should she not have been operated on at the beginning?

DR. WELCH: The point is that when she was first seen outside she should have been operated on at once. Then she would have been well and been home three weeks earlier. As time went on her condition became worse, and operation without preparation might have been fatal.

DR. EARLE M. CHAPMAN: I am sorry to have arrived late for this discussion, but perhaps I can clarify things a bit. This woman was quite well until a Sunday night when she drank the sour cocktails at 6:00 and then had the agonizing abdominal pain that started about 10:00. I was awakened to see her at midnight, and the first thing I considered was gastritis severe enough to cause erosion or even perforation, but she had had such a normal abdomen without any scar on it that even a surgeon would have hesitated to operate at that time. I returned to Boston and she, being a Christian Scientist, was attended by the healer several times, but when fecal vomiting appeared the family overruled faith treatment and called in a neighborhood surgeon, who advised immediate operation. The family telephoned me — hospitalization here was advised, and I still think that the four-day delay in operation was wise treatment. At entry she was sick and vomiting and had an elevated nonprotein nitrogen and a low blood chloride; with supportive treatment she was in much better condition and made an amazing postoperative recovery.

CASE 32432

PRESENTATION OF CASE

A twenty-year-old girl entered the hospital complaining of a tumor on the collar bone of one month's duration.

The patient stated that she had always been in excellent health until about a month before entry, when she noted a small swelling located at the right sternoclavicular junction that was not tender or red and had not bothered her. It had increased rather rapidly in size, until it reached the size of a golf ball. There had been no weight loss.

Physical examination revealed a well developed and well nourished obese girl who did not appear ill. Positive physical findings were limited to the skin and the right clavicle, where there was a hard tumor, about the size of a golf ball, located on the superior portion just lateral to the sternoclavicular joint. It was slightly movable and was less hard on top than at the base, seeming to be attached to the clavicle.

The temperature was normal, and the blood pressure was 90 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 5,020,000, with 97 per cent hemoglobin and a white-cell count of 7500, with 52 per cent neutrophils, 38 per cent lymphocytes, 7 per cent monocytes and 3 per cent eosinophils. The red cells and platelets were normal. The blood Hinton test was negative.

X-ray films of the right clavicle revealed a destructive lesion, involving the proximal 5 cm. of the clavicle with destruction of the cortex in the involved area, which extended up to the sternoclavicular junction. A film of the chest showed the lungs to be clear.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ERNEST M. DALAND: The physical examination was essentially negative, with the exception of the lesion over the clavicle, which was revealed, on x-ray examination, to involve the clavicle. I believe that it comes down to a differential diagnosis of conditions arising in the clavicle.

May we see the x-ray films?

DR. JAMES R. LINGLEY: This is the lesion involving the medial end of the clavicle. I cannot add anything to the description given in the record. It appears to be destructive and has broken through the cortex.

DR. DALAND: Is there destruction of the upper cortex?

DR. LINGLEY: I think that there is probably destruction all the way through.

DR. DALAND: Has the lesion broken through the end of the bone?

DR. LINGLEY: The articular cortex looks intact. It has broken through anteriorly.

DR. DALAND: We must consider inflammatory lesions and tumor. The inflammatory lesions that could be involved include osteomyelitis, which I think we can rule out, since the white-cell count was normal and the patient was in fairly good general physical condition. Tertiary syphilis must be thought of immediately, because this is a frequent position for a gumma. The blood Hinton test was negative, and that fairly well rules out that diagnosis. Tuberculosis should also be considered, but it seems to me that one would expect to find complete destruction of the clavicle, including penetration through the articular surface. I think that a tuberculous process would have worked in around the sternoclavicular joint rather than have projected out as an external tumor. I believe that we can rule out any inflammatory condition.

The tumors most frequently encountered in the clavicle are probably the giant-cell tumors. In a giant-cell tumor one expects to find an expansile tumor with nearly equal vertical and horizontal diameters. Signs of expansion of the bone would have been observed before any break in the cortex, and the history would probably have been longer

than one month with symptoms. I think that we can rule out giant-cell tumor. An enchondroma could have occurred but again I think that there would have been evidence of bone expansion before rupture of the cortex, as well as a more distinct outline of the tumor. Osteogenic sarcoma is always a possibility in any bone; there is no bone where it cannot occur. The appearance of this lesion is suggestive of it, in that there was a break in the cortex on both sides, with an external tumor mass. There was no ray formation that I can make out and that is one of the characteristic signs of osteogenic sarcoma. There are no typical signs in an early case, however, and osteogenic sarcoma is a distinct possibility. I doubt that an eosinophilic granuloma would have produced an external tumor mass of this size with a bone lesion no larger than this. There is no note that there was any expansile pulsation, such as one expects in hemangioma destroying bone, and the external surface did not suggest hemangioma. We must consider metastatic cancer. Carcinoma of the breast can metastasize to the clavicle, as can many other types of carcinoma. This girl was only twenty, however, and the chances are against it. Physical examination apparently did not reveal any other disease suggesting a primary focus, and I think that metastatic carcinoma can be ruled out.

The probability is that this was a lymphoma. Lymphoma does occur in the clavicle as a solitary lesion. I recall a solitary lymphoma of the midportion of the clavicle that I resected about twelve years ago. I inserted a bone graft, and the patient remained well with no secondary lymphoma. The physical examination in the case under discussion also did not show any other sign of lymphoma. My belief is that this will turn out to be a lymphoma.

Dr. Lingley: I should like to ask Dr. Daland if he would consider a Ewing tumor?

Dr. Daland: Yes; Ewing tumor should certainly be considered, and I cannot rule it out.

Dr. Tracy B. Mallory: What was your diagnosis, Dr. Lingley?

Dr. Lingley: I thought that it was either Ewing tumor or lymphoma, and I put the former first.

Dr. Mallory: Dr. Hare, you originally read these films. What did you think about them?

Dr. Hugh F. Hare: I thought that it was a lymphoma and put Ewing tumor second.

Clinical Diagnosis

Lymphoma of clavicle.

Dr. Daland's Diagnosis

Lymphoma of clavicle.

Anatomical Diagnosis

Ewing tumor of clavicle.

Pathological Discussion

Dr. Mallory: The operation mentioned in the record, at the point where the abstract terminates, was a biopsy, which showed a characteristic picture of a Ewing tumor. The patient was then given x-ray treatment by Dr. Hare. Perhaps he will tell us about that stage of the progress.

Dr. Hare: When I first saw the patient following the biopsy, the swelling was considerably larger than a golf ball, being about the size of a lemon. We started treatment with large daily doses of 350 r, a total of 2800 r being given to the skin. It caused a skin reaction, and at that time we discontinued treatment. I saw the girl six weeks later, when the tumor had decreased somewhat in size.

Dr. Mallory: About two months following the x-ray treatment the patient again entered this hospital, and it was decided to resect the clavicle. That was done, and I have a photograph (Fig. 1) that I shall show you. The proximal end of the clavicle lies

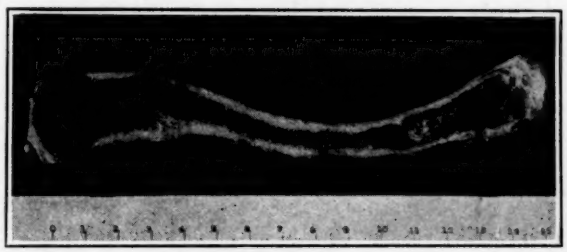

Figure 1.

to the right. A large cystic cavity filled with blood and necrotic tissue can be seen. We made many sections throughout that area. We were unable to find any remaining trace of tumor. So far as the morphologic evidence is concerned, the x-rays had apparently completely destroyed the neoplasm.

One always has the alternative of x-ray treatment or surgery in these cases. Does anyone wish to express an opinion in this case? This patient was given a double chance, since she received both forms of treatment in succession.

Dr. Grantley W. Taylor: This patient's family was anxious that something further be done if possible to improve her chance of cure, because the prognosis given to them following biopsy and x-ray treatment had been pessimistic. Since the tumor was still present and the x-ray evidence of destruction showed a continuing process in the clavicle, it seemed worth while to consider excision of the clavicle. The skin had recovered from the initial radiation reaction and had not yet undergone the late changes that jeopardize healing following surgery through a radiated area. With these facts in mind, the entire clavicle was removed, including the periosteum and the muscular attachments. The pa-

tient made an excellent recovery from operation, and the wound healed primarily. She has returned to work and has excellent function of the arm. There is no evidence of metastasis or recurrence at the present time.

DR. RICHARD H. WALLACE: I should like to ask about the possibility of recurrence with this sequence if the clavicle had not been removed. What assurance is there that there might not have been a few viable cells?

DR. MALLORY: Frankly speaking, none. It would be impossible to rule that out with certainty. That there had been massive and apparently complete destruction of tumor is all that I can say.

DR. WALLACE: Would there be reasonable assurance that it might not recur, since there was no microscopic evidence of tumor?

DR. MALLORY: I should prefer to have a radiologist's opinion. It is my impression that, in a fair number of these cases treated by x-ray, there has been no recurrence even in the face of metastases. Is that correct?

DR. LINGLEY: Yes; we have had several such cases.

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Established 1828

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"A HUNDRED YEARS AGO"

It has long been a custom of certain of our esteemed, if more youthful, contemporaries, particularly those addicted to the daily dissemination of current events, to publish a department that comments briefly on the happenings of an otherwise forgotten era. Thus each day there appears in subdued tones, betokening the softening influence of time, the abbreviated news stories of a quarter century ago, reminding the reader that there has been a past, however colorless, in addition to a troublesome present and a hypothetical future. In view of these attempts to link the present with the past, the *Journal*, sturdy survivor of a hoarier age, — for even the *Boston Herald* came in only with ether, — has decided to make its own contribution to this factual anthology: with its scarcely rivaled opportunities for chronological research, it has determined to dig more deeply into the archives of antiquity and bring forth from time to time, or at approximately lunar intervals, brief excerpts from its own files of a century ago.

The first article of the series appears elsewhere in this issue of the *Journal*, and it should be noted that the leading item in these abstracts of October, 1846, comments on that anesthetizing preparation with the aid of which, no doubt, our previously mentioned young journalistic contemporary was eaned. Even then, the *Journal* was in the fore with the publication of medical discoveries of importance. Some of these excerpts deal with truths that seem to be permanent, which is less often the case with scientific advances than it is with some of the basic principles of our art. Thus, with the reference to the poor chirography among medical men, this is as true today as it was a century ago, and is due, obviously, to the policy of putting it up to the apothecary to compound the prescription the way it ought to be.

These miscellaneous abstracts will serve other purposes than to entertain and to amuse. They will remind us that former days have had their pioneers, their heroes, their men of stature; that the achievements of today are built on the foundations that untold centuries of achievement laid down. While we are entertained, let us also be chastened, for one day we, too, will be of a century that has passed.

The *Journal* is fortunate in that Dr. Reginald Fitz has consented to compile this column. A student of medical history, Dr. Fitz brought to his term of office as president an unusual devotion to the interests of the Massachusetts Medical Society, as well as a knowledge of its traditions.

THE PATIENT AND THE TRUTH

The question whether a patient with malignant disease should be told the truth, the whole truth and nothing but the truth is not easy to answer. The

subject is thoroughly discussed in two papers in the June issue of the *Annals of Internal Medicine*.[1, 2]

The chief difficulties in answering this question arise from the facts that the psychologic make-up of one patient differs from that of another, that legal responsibility is involved and, finally, that the physician himself does not always know what is the truth — the best may be mistaken. A family will forgive him if he says that the patient is going to live and the patient subsequently dies — for all men die; but the physician will never be forgiven if he predicts without qualification a fatal outcome and the patient then proceeds to get well. Furthermore the intricacies of medical terminology are such that the doctor is often forced — in telling the truth — to use lay terms that are, in themselves, scientifically inaccurate to convey to the patient his idea of the truth, and thereby he may defeat his own purpose and end merely by confusing or, from a legal point of view, by misleading the patient.

Certain principles seem reasonably well established. Some responsible friend or relative of the patient must be apprised of the facts in so far as they are known. No operation, unless it be an emergency life-saving measure, may be done without the patient's consent. No misstatement of facts or evasive answers may be given if the purpose is to serve the physician's personal interests or financial gain, nor may an operation be performed for like reasons. A physician may be liable if he makes a positive but erroneous diagnosis. It is rather generally agreed that a doctor suffering from one or another form of malignant tumor should be so told, but from this point on there is no unanimity of either legal or non-legal opinion regarding how much or how little should be said.

It may seriously be questioned whether it "usually does good to patients to tell them that the outlook is hopeless."[1] It seems truer that "an insight gained gradually . . . is less likely to cause intense mental anguish than knowledge gained abruptly of one's imminent demise."[2] A few there are who can face the truth with equanimity. There are some, of course, who must be told the truth because their personal or professional responsibilities are such that their affairs must be put in order. But even here, if some responsible member of the family or some close friend has been informed about the facts, it is not often that the patient need be directly told by the physician.

It may be necessary or advisable to tell a given patient that he has cancer in order to persuade him to undergo what is believed to be the necessary therapeutic measures; but at the same time the word "cancer" may so frighten a patient that he refuses treatment, — so imbued is the lay mind with the idea that cancer is incurable, — and the use of such a word as "tumor" or "mass" often serves better to adjust the patient's therapeutic future.

The question whether a physician if asked by a patient with cancer "Have I cancer?" must necessarily answer "Yes" is a moot one. It is doubtful whether a suit would lie were the physician to skillfully by-pass the question, provided, of course, that some responsible member of the family knew the facts.

The question of prognosis is also a difficult problem. At best one can deal in broad generalities. Neither the average nor the mean necessarily applies to the individual case unless the extremes are so close to each other that the difference is negligible. A patient with malignant or pseudomalignant disease is usually satisfied with the statement that the condition is a serious one, that certain therapeutic measures are advisable and that benefit will accrue. As time passes the patient either fails progressively without fully realizing it or, by himself, comes to recognize that he will have the disease all his life. From that point the transition to a realization that he will die of the selfsame disease is an easy one, and the experienced physician is able to tell when such knowledge has been gained. When it has, the patient seldom speaks of it; the doctor need not.

If a physician has followed a course sincerely designed for the patient's best interests, if he has told some responsible person the facts and if he has informed the patient that the condition is a serious one, no court would judge him derelict in his duty.

References

1. Lund, C. C. Doctor, patient, and truth. *Ann. Int. Med.* 24:955-959, 1946.
2. Smith, W. S. Legal privilege, on therapeutic grounds, to withhold specific diagnosis from patient sick with serious or fatal illness. *Ann. Int. Med.* 24:960-967, 1946.

A HUNDRED YEARS AGO

Strange stories are related in the papers of a wonderful preparation in this city, by administering which a patient is affected just long enough and just powerfully enough to undergo a surgical operation without pain. — Benjamin Waterhouse, M.D., died recently at the patriarchal age of ninety-two at his residence in Cambridge. During the active part of his life very few physicians have held a more conspicuous place in the public observation. A lecture which he delivered about 1805 to the Harvard undergraduates on the custom of smoking cigars is supposed to have had great influence in whatever diminution of that practice was consequent on its publication. He was an early and decided advocate for the introduction of the practice of vaccination into this country and always esteemed it one of his proudest laurels that he was designated the American Jenner. — Cholera morbus is spoken of as being quite fatal in the eastern part of New Hampshire. — As a fraternity medical men are proverbial for their bad writing. Some of the manuscripts sent to us would puzzle the chirographical professor to determine whether they were written in English, Chinese or Cherokee. A physician who cannot write should not be allowed to practise; and a man who can write and only scrawls should be regarded as committing a criminal offence. — Dr. Daniel Drake, of Cincinnati, reports: "I have lately assisted in the *post mortem* examination of two patients who died after several weeks of illness with symptoms answering well to Louis' description of Typhoid Fever. This fever may be among our increasing diseases. If so, it is entitled to great attention; just as an invading army should be more vigilantly watched than one which is retreating. Can anyone tell whether those cases of remittent bilious fever which in their latter stages exhibit typhoid symptoms are accompanied by lesions of the ileum?" — A boy seven years old swallowed an open penknife three inches long. The symptoms afterwards were slight. The treatment enjoined was perfect quietude, fomentations, saline febrifuges, sedatives, the occasional exhibition of slight aperients, castor oil etc. On the morning of the sixth day the knife appeared with an evacuation, blade downward, somewhat corroded and not at all improved in appearance by its change of residence. — The increasing population of Boston demands corresponding charities to meet the necessities of the sick and infirm poor. A conviction that another infirmary was required led to the recent opening of one at 425 Washington Street. This is to be open at all hours so that those who are least able to walk from a remote section of the town will be certain of finding someone to give them desired advice. John B. Walker, M.D., takes charge of the department of surgery; C. E. Buckingham, M.D., E. H. Clarke, M.D., S. Kneeland, M.D., and W. Henry Thayer, M.D., will in turn be in attendance in the management of the medical labors. All operations will be performed gratuitously when necessary and bandages, apparatus etc. freely given. — A lady ninety years of age residing at Cold Spring has recently cut four front teeth, being the third set, and her eye-sight has so far returned that she can see without glasses. — Some villain has discovered a new agent of iniquity in the way of drugging cigars with narcotics. A boy of five picked up a cigar partly smoked and gave it to a journeyman tailor. He lighted it but after a few puffs, experiencing some uneasy sensations in his head, threw it down. The little boy then tried it, exhibited all the symptoms of violent poisoning and died eighteen hours later. Three professional gentlemen who saw him opined that the cigar had been drugged with some virulent narcotic. — A new remedy for strangury is announced. Take 40–60 bees in a tea-cup, pour one gill of boiling water on them and cover the cup securely. When it has stood for about twenty minutes, pour off the infusion and let the patient take the whole as a draught. It is supposed that the material which gives efficacy to the bee tea is the virus ejected by its sting. It remains to be seen whether this virus may not be collected and preserved so as to be employed when the bee itself is not to be obtained. — A barrel containing several parts of a human skeleton was found floating in the upper basin of the Mill Dam, Boston, by some boys last week. — A Swiss journal states that the bulb of the dahlia when dressed like the potato affords an excellent article of food. — We perceive that Medical Societies in several States have already elected delegates to the great convention to be holden in Philadelphia in May next. If we may judge from the spirit manifested at the last convention, we presume that medical men of respectability who may be present will not only have seats accorded to them but the liberty of discussion if they desire it. — Extracted from the *Boston Medical and Surgical Journal*, October, 1846.

R. F.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATH

WIGGIN — Henry M. Wiggin, M.D., of Whitefield, died June 29. He was in his seventy-eighth year.

Dr. Wiggin received his degree from Boston University School of Medicine in 1895.

His widow and two sons survive.

MISCELLANY

DR. BARTON AWARDED LEGION OF MERIT

Dr. Walter E. Barton, superintendent of the Boston State Hospital, was recently awarded the Legion of Merit Medal for his work with the Office of the Surgeon General in the rehabilitation of Army patients. Active for fifteen years in the Massachusetts State Medical Service as a psychiatrist, Dr. Barton received the award for his work in organizing and developing the reconditioning program for convalescing patients. As a lieutenant colonel in the Army Medical Corps, his specific services in shaping the doctrine and policy of the four interrelated services of occupational therapy were instrumental in furthering Army medical care.

NOTE

Dr Lloyd C. Fogg, formerly associate professor of microscopic anatomy, Boston University School of Medicine, has been appointed registrar of the School. Dr. Fogg assumed his new duties at the beginning of the current academic year.

CORRESPONDENCE

ERRATUM

To the Editor: I wish to call attention to an error that crept into my manuscript "Surgery of the Innominate Artery," which was published in the July 18 issue of the *Journal*.

On page 74, near the bottom of the first column, I referred to "Burrell, of Philadelphia." Actually, Dr. Burrell was a clinical professor of surgery at Harvard and a resident of Boston. The error came about because the transcription in which his case was published was for the meeting of the American Surgical Association held in Philadelphia in 1895. Dr. David Cheever pointed out this error to me.

789 Howard Avenue
New Haven, Connecticut

GUSTAF E. LINDSKOG, M.D.

NOTICES

ANNOUNCEMENTS

Dr. Edward A. Adams announces that Dr. Robert S. Thomson is associated with him for the practice of general surgery at 44 Oliver Street, Fitchburg.

Dr. Norman H. Boyer, having returned from military service, announces the reopening of his office at 29 Bay State Road, Boston.

Dr. Thomas E. Chretien has returned from naval service and announces the opening of an office for the practice of general medicine at 435 Wolcott Street, Auburndale.

Dr. Clito R. Damiani announces the opening of an office at 16 Norwich Street, Worcester, for the practice of dermatology.

Dr. William H. Holtham, having returned from military service, announces the reopening of his office for the practice of urology at 270 Commonwealth Avenue, Boston.

Dr. Philip A. Isaacson, having returned from military service, announces the opening of his office for the general practice of medicine at 717 Main Street, Fitchburg, Massachusetts.

Dr. G. S. Nossiff, having returned from military service, announces the opening of an office at 38 Congress Street, Milford, succeeding Dr. Perry E. Joslin.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, November 5, at 8:15 p.m. Dr. Reginald H. Smithwick will speak on the subject "Operative Measures for the Relief of Hypertension."

CUTTER LECTURE

The Cutter Lecture on Preventive Medicine will be given by Sir Lionel Whitby, Regius Professor of Physic, University of Cambridge, England, at 5 p.m. on Wednesday, November 6, in the Amphitheater of Building D of the Harvard Medical School. His subject will be "The Hematological Effects of Irradiation."

The medical profession, medical and public-health students and others interested are cordially invited to attend.

SUFFOLK DISTRICT MEDICAL SOCIETY

The fall dinner meeting of the Suffolk District Medical Society will be held at the Harvard Club of Boston on Saturday, November 9, at 7:00 p.m. Dr. Shields Warren will speak on "The Physiological and the Pathological Effects of the Atomic Bombs," and Dr. Joseph C. Aub will speak on "Isotopes in Clinical Research."

Members of the district society and their wives, as well as young people of high-school and college age whose parents are members, are cordially invited to attend. Tickets for the dinner and cocktails ($3.00 per person) must be purchased in advance by sending cash or a check to Dr. Richard S. Eustis, 319 Longwood Avenue, Boston 15, before November 2. After this date other members of the Massachusetts Medical Society, their wives and young adult members of their families, may apply. Cocktails will be served at 6.30 p.m.

AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

The third American Congress on Obstetrics and Gynecology will be held September 8 to 12, 1947, in St. Louis, Missouri. All the meetings and the scientific and technical exhibits will be held in the Municipal Auditorium.

Although the third congress is similar in scope and program to the two previous meetings, it will be larger in every way. The program is being made up to appeal to specialists in obstetrics and gynecology, to general practitioners interested in those fields, to hospital administrators and to nurses, as well as to public-health physicians and nurses.

The morning sessions of the congress on September 12 will be given over entirely to the National Federation of Obstetric-Gynecologic Societies. An evening speaker of nationwide prominence will present his viewpoints to a joint meeting of the congress, the federation and the general public.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 31

FRIDAY, NOVEMBER 1

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, NOVEMBER 4

*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, NOVEMBER 5

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

8:15 p.m. Greater Boston Medical Society. Auditorium, Beth Israel Hospital.

(*Notices continued on page xv*)

NOTICES (*Continued from page 636*)

WEDNESDAY, NOVEMBER 6

*10:30–11:30 a.m. Medical Clinic. Isolation Building Amphitheater. Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

5:00 p.m. Cutter Lecture. Amphitheater of Building D, Harvard Medical School.

*Open to the medical profession.

OCTOBER 4–30. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Page 532, issue of October 3.

OCTOBER 11–MAY 14. Metropolitan State Hospital. Page 398, issue of September 12.

OCTOBER 15–DECEMBER 5. Exhibition in Commemoration of Ether Centenary. Page 570, issue of October 10.

OCTOBER 30. New England Obstetrical and Gynecological Society. Page 532, issue of October 3.

NOVEMBER 5. Greater Boston Medical Society. Page 636.

NOVEMBER 6. Cutter Lecture. Page 636.

NOVEMBER 9. Suffolk District Medical Society. Page 636.

NOVEMBER 12. Harvard Medical Society. Amphitheater. Peter Bent Brigham Hospital. 8:00 p.m.

NOVEMBER 12–14. American Public Health Association. Cleveland.

NOVEMBER 14. Rectal Bleeding, Its Significance and Treatment. Dr. E. Parker Hayden. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

NOVEMBER 20. New England Oto-Laryngological Society. Page 532, issue of October 3.

NOVEMBER 25–27. American Academy of Allergy. Page 570, issue of October 10.

DECEMBER 5. Suffolk Censors' Meeting. Page 346, issue of September 5.

DECEMBER 7–12. American Academy of Dermatology and Syphilology. Page 570, issue of October 10.

FEBRUARY 7. American Board of Obstetrics and Gynecology. Page 238, issue of August 15.

APRIL 28–MAY 2. American College of Physicians. Page 206, issue of August 8.

SEPTEMBER 8–12. American Congress on Obstetrics and Gynecology. Page 636.

DISTRICT MEDICAL SOCIETIES

PLYMOUTH

NOVEMBER 21. Plymouth County Hospital, South Hanson.

JANUARY 16. Brockton Hospital, Brockton.

FEBRUARY 20. Moore Hospital, Brockton.

MARCH 20. Goddard Hospital, Brockton.

APRIL 17. State Farm, Bridgewater.

MAY 15. Lakeville Sanatorium, Lakeville.

SUFFOLK

NOVEMBER 9. Dinner meeting. Page 636.

DECEMBER 5. Censors' meeting. Page 346, issue of September 5.

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